

Brazilian Guideline for Heart Failure – 2026

Diretriz Brasileira de Insuficiência Cardíaca – 2026

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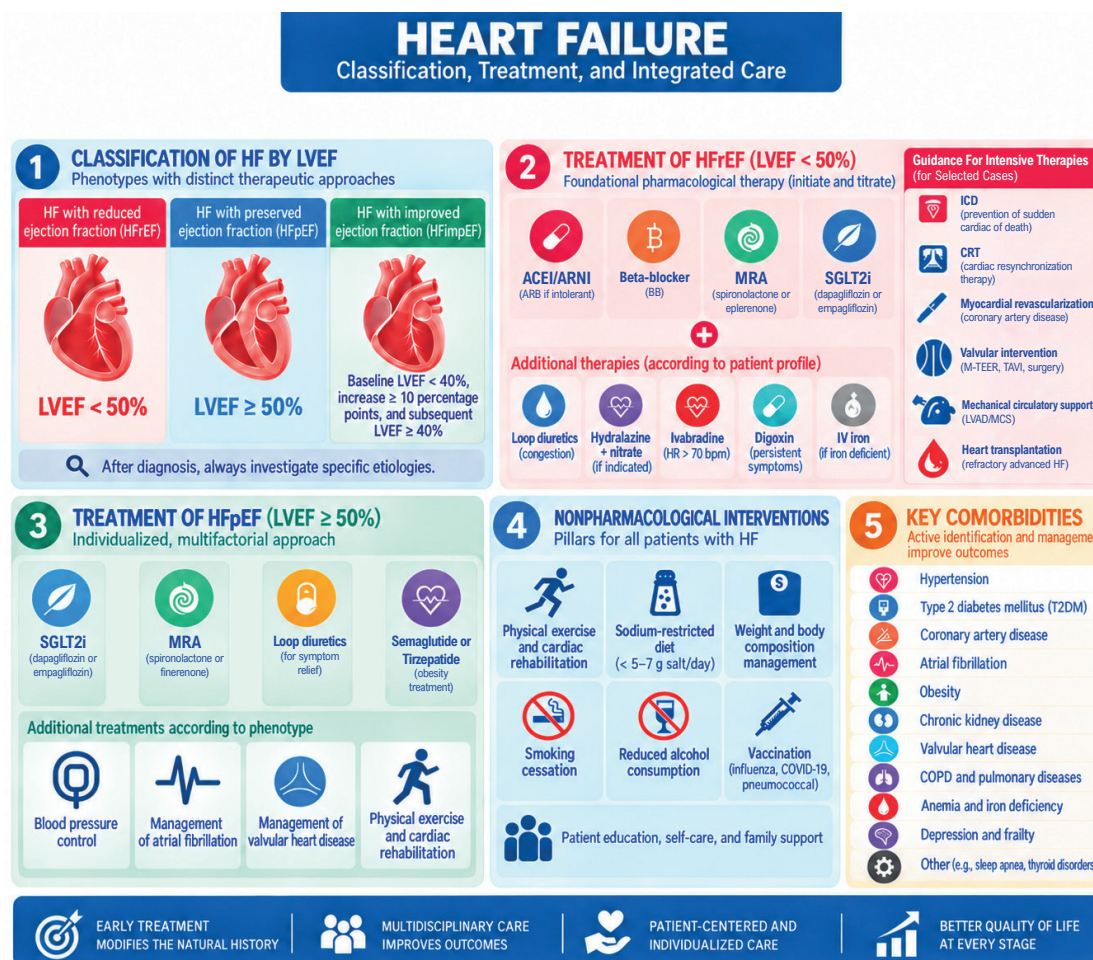
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Central Illustration: Brazilian Guideline for Heart Failure – 2026



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ARB: angiotensin receptor blocker; RBBB: right bundle branch block; LBBB: left bundle branch block; ICD: implantable cardioverter-defibrillator; NYHA: New York Heart Association functional class; AF: atrial fibrillation; HR: heart rate; LVEF: left ventricular ejection fraction; H+N: hydralazine plus nitrate; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; ACEI: angiotensin-converting enzyme inhibitor; ARNI: angiotensin receptor-neprilysin inhibitor; SGLT2i: sodium-glucose cotransporter 2 inhibitor; RAASi: renin-angiotensin-aldosterone system inhibitor; CRT: cardiac resynchronization therapy.

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1. Introduction

Heart failure (HF) is a complex clinical syndrome with a high prevalence, substantial mortality, and a profound impact on patients' quality of life. Since the publication of the latest Brazilian guidelines for acute and chronic HF in 2018,¹ major advances have been achieved in the diagnosis, treatment, and monitoring of patients with HF, particularly those with HF with preserved ejection fraction (HFpEF). In parallel, the past decade has witnessed remarkable progress in precision medicine, including the development of novel therapies capable of altering the natural history of several forms of cardiomyopathy, as well as continuous improvements in multimodality cardiovascular imaging techniques.

These advances underscore the need to update the Brazilian guidelines for acute and chronic HF, as a tool to guide clinical practice, providing evidence-based recommendations while considering the balance of benefits and risks, as well as the feasibility of implementing the available diagnostic and therapeutic strategies (Central Illustration).

Consistent with the approach adopted by several international cardiology societies and with a commitment to the most rigorous appraisal of the scientific evidence, this guideline was developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system² to assess the certainty of evidence and strength of recommendations. According to the GRADE framework, recommendations may be classified as STRONG or WEAK, either IN FAVOR OF or AGAINST an intervention, whereas the certainty of evidence ranges from HIGH to VERY LOW. Chart 1.1 summarizes the key factors considered in determining the strength of recommendations, and Chart 1.2 summarizes the factors used to assess the certainty of evidence. Accordingly, a color-coding system is used throughout this guideline in the recommendation tables to indicate the strength of recommendations and certainty of evidence, as shown in Chart 1.3.

2. General Considerations

2.1. Definition of Heart Failure

HF is a multifactorial clinical syndrome resulting from a variety of etiologies and underlying pathophysiological mechanisms. A recent consensus statement developed by international cardiology societies proposed a universal definition of HF.³

Chart 1.1 – Criteria used to determine the strength of recommendations

Strength of recommendation	Criteria
STRONG	– High certainty of evidence – Benefits clearly outweigh risk and burdens – Low cost – No alternative options
WEAK	– Low or very low certainty of evidence – Benefits closely balanced with risk and burdens – High cost – Other equivalent options

According to this definition, HF is characterized as a clinical syndrome with:

- Current or prior typical symptoms and/or signs (Chart 2.1) caused by a structural and/or functional cardiac abnormality; and
- Elevated natriuretic peptide (NP) levels or objective evidence of cardiogenic pulmonary or systemic congestion by diagnostic modalities such as imaging (eg, chest radiography or elevated filling pressures by echocardiography) or hemodynamic measurement (at rest or with provocation).

This updated definition underscores the need for an integrated diagnostic approach that combines careful clinical assessment with biochemical and imaging findings, enabling a more accurate, reproducible, and useful characterization of HF in clinical and research settings. The diagnostic algorithm for HF (Figure 3.1) incorporates these concepts.

2.2. Main Signs and Symptoms

A thorough medical history and comprehensive physical examination are key components of the initial evaluation of HF. The primary objectives are to identify signs and symptoms suggestive of clinical congestion and/or low cardiac output (Chart 2.1).^{1,4} It is important to recognize that no individual sign or symptom has sufficient sensitivity and specificity to establish the diagnosis of HF. Nevertheless, some findings are relatively more specific for congestion, including a third heart sound (gallop rhythm), elevated jugular venous pressure, orthopnea, and paroxysmal nocturnal dyspnea.⁵

Chart 1.2 – Summary of the criteria used to assess the certainty of evidence

Certainty of evidence	Definition	Source of evidence
HIGH	We are very confident that the true effect lies close to that of the estimate of the effect.	– Well-designed randomized controlled trials with representative samples. – Methodologically robust meta-analyses. – In some cases, well-designed observational studies with consistent findings.
MODERATE	We are moderately confident in the estimate of effect.	– Randomized controlled trials with minor limitations. – Well-designed observational studies with consistent findings.
LOW	Our confidence in the effect is limited.	– Randomized controlled trials with moderate limitations. – Comparative observational studies: cohort and case-control.
VERY LOW	We have very little confidence in the estimate of effect. There is major uncertainty in the findings.	– Randomized controlled trials with major limitations. – Comparative observational studies with limitations. – Non-comparative observational studies. – Expert opinion.

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Chart 1.3 – Color-coding system for the strength of recommendations and certainty of evidence

STRENGTH OF RECOMMENDATION	STRONG	CERTAINTY OF EVIDENCE	HIGH
	WEAK		MODERATE
			LOW
			VERY LOW

2.3. Classification of Heart Failure According to Left Ventricular Ejection Fraction

Left ventricular ejection fraction (LVEF) is a central parameter in HF, guiding prognostic stratification and therapeutic decision-making.³ Despite its importance, assessment of LVEF in isolation is inherently limited, as other imaging modalities may provide additional relevant information for phenotypic characterization. Nevertheless, there is currently a consensus that an LVEF cutoff of 50% should be used to define a significant reduction.⁶ (Chart 2.2)

Patients with a left ventricular ejection fraction (LVEF) $\geq 50\%$ are classified as having heart failure with preserved ejection fraction (HFpEF). Terms such as “normal LVEF” and

“diastolic heart failure” have been progressively abandoned. This reflects the recognition that many of these patients exhibit detectable systolic dysfunction when assessed using parameters other than LVEF, while diastolic dysfunction is also commonly observed in patients with heart failure with reduced ejection fraction (HFrEF), thereby limiting its value as a discriminating feature.

In this guideline, the term heart failure with mildly reduced ejection fraction (HFmrEF), previously used to describe patients with an LVEF between 41% and 49%, has been omitted, as this population shares several clinical characteristics and demonstrates therapeutic responses comparable to those of patients with reduced ejection fraction. Furthermore, this condition appears to represent a transitional phase along the trajectory of ejection fraction rather than a distinct clinical phenotype.

Accordingly, the term heart failure with improved ejection fraction (HFimpEF) remains appropriate, acknowledging the potential for substantial reverse remodeling with contemporary heart failure therapy.

2.4. Classification According to Symptom Severity – Functional Classes

The New York Heart Association (NYHA) functional classification is a clinical tool used to assess symptom severity in patients with HF based on the degree of limitation imposed on physical activity. It is a subjective assessment performed by the clinician and should be regarded as a dynamic parameter that may change over the course of the disease. Consequently, its subjective nature imposes

Chart 2.1 – Main signs and symptoms of heart failure

Typical symptoms	More specific signs
Dyspnea	Elevated jugular venous pressure
Orthopnea	Hepatojugular reflux
Paroxysmal nocturnal dyspnea	Third heart sound or gallop rhythm
Fatigue and slower recovery after exercise	Apical impulse displaced to the left
Exercise intolerance	
Nocturnal cough	Cachexia
Palpitations	Pulmonary rales
Bendopnea	Pleural effusion
Postprandial satiety	Cheyne–Stokes respiration
Weight gain (> 2 kg/week)	Tachycardia
Weight loss (advanced HF)	Hepatomegaly
Loss of appetite	Ascites
Nocturia and oliguria*	Cold extremities*
Confusion/syncope*	Peripheral edema

*Signs/symptoms that may indicate low cardiac output.
HF: heart failure.

Chart 2.2 – Classification of heart failure according to ejection fraction

Classification	Abbreviation	LVEF criterion
HF with reduced ejection fraction	HFrEF	< 50%
HF with preserved ejection fraction	HFpEF	$\geq 50\%$
HF with improved ejection fraction	HFimpEF	Baseline LVEF < 40%, with an increase of ≥ 10 points from baseline and a second measurement showing LVEF $\geq 40\%$

LVEF: left ventricular ejection fraction; HF: heart failure.

limitations on its accuracy. The NYHA functional class is an independent predictor of mortality⁷ and is widely used in clinical practice to determine patient eligibility for multiple therapeutic strategies. It also serves as a standard measure for evaluating response to HF treatment, allowing clinicians to monitor improvements in functional status or, conversely, to identify disease progression.

According to exercise tolerance, the NYHA classification ranges from class I, indicating no HF-related symptoms, to class IV, characterized by symptoms with minimal exertion or at rest (Chart 2.3). Given the limited reproducibility and subjective nature of this classification, particularly when distinguishing between NYHA classes I and II,⁸ it has been proposed that the medical history should include specific questions regarding the patient's ability to perform activities with known metabolic costs.⁹

2.5. Classification According to Disease Stages/Progression

The staging system proposed by the American College of Cardiology/American Heart Association (AHA/ACC)¹¹ emphasizes the development and progression of structural heart disease and symptoms (Figure 2.1). This framework comprises 4 stages of HF. Stage A includes patients at risk for HF but without structural heart disease, such as those with hypertension, cardiovascular disease, diabetes, obesity, or exposure to cardiotoxic medications. Stage B, also referred to as pre-HF, includes patients with evidence of structural heart disease who remain asymptomatic. Stage C includes patients with structural heart disease and current

or previous symptoms of HF.

Among patients in stage C, failure to achieve improvement in symptoms or resolution of structural cardiac abnormalities should be considered an indicator of a worse prognosis and classified as “persistent HF.”

Stage D includes patients with advanced HF who have severe, refractory symptoms requiring specialized interventions, such as heart transplant, ventricular assist devices, or palliative care. The specific management strategies for each stage are discussed in dedicated chapters of this guideline.

2.6. Classification of Heart Failure According to Clinical/Laboratory Trajectory

The identification of a growing number of patients with stage C HF who experience favorable clinical outcome,^{12,13} characterized by sustained clinical improvement and reverse remodeling following optimal guideline-directed medical therapy (GDMT), has highlighted the need for more comprehensive classification systems that integrate clinical, laboratory, and imaging parameters, as recently proposed by an expert consensus of the European Society of Cardiology.¹⁴

Patients with a baseline LVEF $\leq 40\%$ who demonstrate an increase in LVEF of at least 10 percentage points and a follow-up LVEF $> 40\%$ but $< 50\%$, while continuing to exhibit persistent symptoms (NYHA class II–IV), elevated N-terminal pro-B-type NP (NT-proBNP) levels, and persistent structural abnormalities on echocardiography, are classified as having improved HF.

Patients with an initial LVEF $< 50\%$ may subsequently achieve functional recovery, with an increase in LVEF to $> 50\%$, accompanied by symptom improvement and reduction in cardiac biomarkers, characterizing the phenotypes known as HF in remission or recovered HF.

HF in remission is characterized by an initial LVEF $< 50\%$, an increase in LVEF of at least 10 percentage points, and a follow-up LVEF $> 50\%$. Patients are asymptomatic or have mild symptoms (NYHA class I–II), with only minimal residual structural abnormalities on echocardiography and mildly elevated NT-proBNP levels. Recovered HF is defined as an initial LVEF $\leq 50\%$, an increase in LVEF of at least 10 percentage points, and a sustained LVEF $> 50\%$ for at least 12 months, accompanied by normalization of cardiac structure and function, absence of symptoms (NYHA class I), and normal NT-proBNP levels.¹⁴

Chart 2.3 – New York Heart Association functional classification

Functional class	Definition	General description
I	No symptoms	Asymptomatic
II	Presence of symptoms with ordinary physical activity. No symptoms at rest.	Mild symptoms
III	Presence of symptoms with mild exertion, but remains comfortable at rest.	Moderate symptoms
IV	Inability to carry on any physical activity without discomfort. Symptoms can be present even at rest.	Severe symptoms

Source: adapted from *The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels.*⁹

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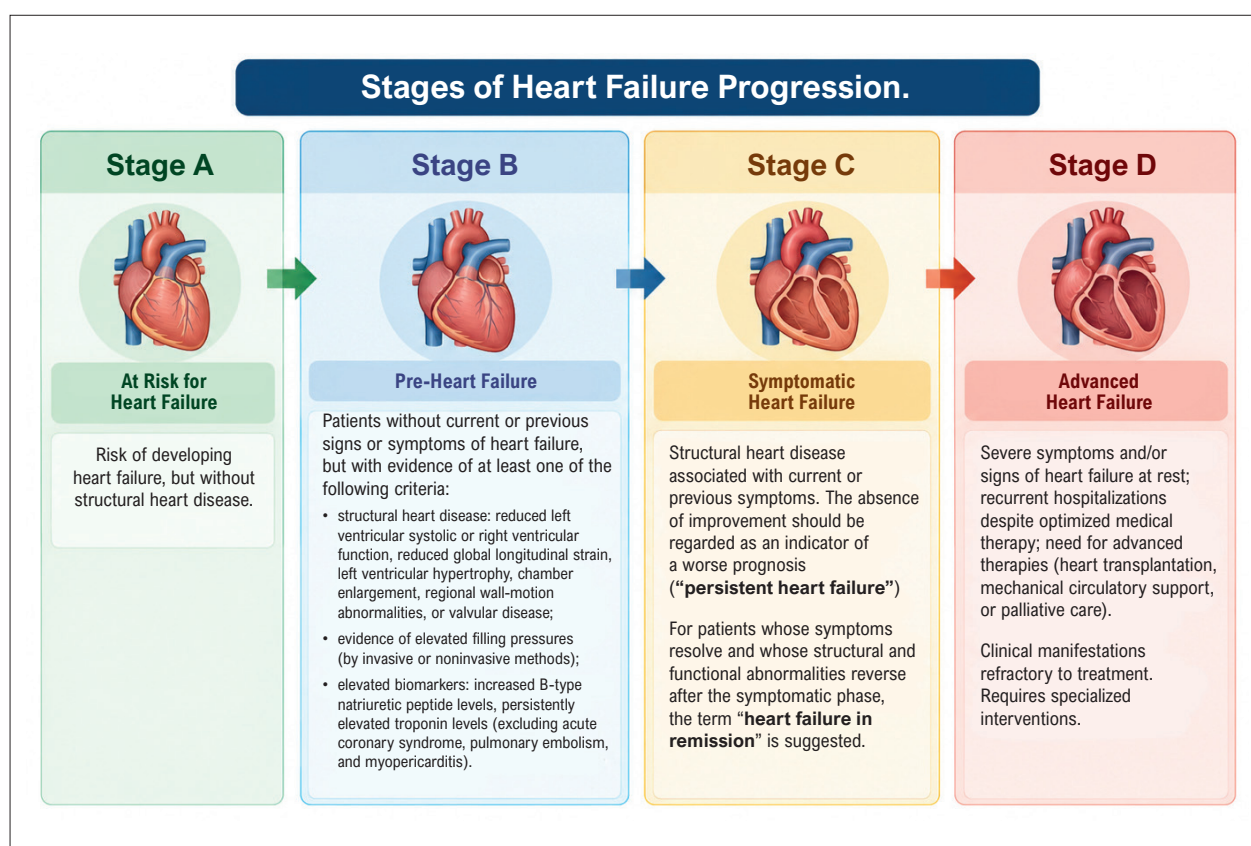


Figure 2.1 – Stages of Heart Failure Progression.

2.7. Other Classifications

2.7.1. Right Ventricular Dysfunction and Right Heart Failure

Right ventricular (RV) dysfunction is defined as impairment of one or more RV functional parameters, most commonly identified by cardiac imaging. RV function is strongly influenced by ventricular interdependence and RV–pulmonary artery coupling, both of which play central roles in a variety of clinical settings. RV dysfunction may be asymptomatic or present with a broad spectrum of clinical manifestations and is an important marker of poor prognosis, with a direct impact on patient morbidity and mortality.¹⁵

Right HF is a clinical syndrome resulting from structural and/or functional abnormalities of the RV. LV failure remains the most common cause of right HF, often associated with secondary pulmonary hypertension. However, there are several conditions in which primary RV abnormalities are the main etiology.¹⁶

2.7.2. Chronic Heart Failure and Decompensated Heart Failure

On the other hand, decompensated HF (DHF) is characterized by the sudden onset or worsening of these symptoms, often accompanied by systemic and/or pulmonary

congestion and, occasionally, impaired perfusion. This condition, with a sudden or rapidly progressive course, generally requires immediate therapeutic intervention

2.8. Incidence and Prevalence of Heart Failure

Recent estimates indicate that, in 2021, approximately 57 million people were living with HF worldwide, with projections suggesting a 34% increase over the coming decades.¹⁷ In Brazil, specific data on HF prevalence remain limited because of the country's marked regional, socioeconomic, and ethnic diversity.¹⁸

HF is most prevalent among individuals aged 70 years or older, although increasing rates have also been observed in younger age groups over recent decades.¹⁹ In Brazil, a systematic review of HF in Latin America, which was based predominantly on Brazilian studies, estimated a mean prevalence of 1% in adults.²⁰ According to one of the few population-based studies conducted in Brazil, the estimated annual incidence was 199 cases per 100,000 population.¹⁸

According to the Global Burden of Disease (GBD) study, the age-standardized prevalence of HF in Brazil declined modestly between 1990 and 2017. However, the absolute number of individuals living with HF increased from 0.67 million to nearly 1.7 million, driven primarily by population aging. Prevalence was higher among women, with substantial regional variation.²¹

Age-stratified analyses have indicated a progressive increase in HF prevalence with advancing age. Between 1990 and 2017, there was an increase particularly in individuals aged 15 to 49 years, possibly reflecting the rise in ischemic events within this age group.²¹

2.9. Most Common Etiologies of Heart Failure in Brazil

HF in Brazil has a heterogeneous etiologic profile that reflects regional disparities, socioeconomic determinants, and the coexistence of infectious and chronic diseases.²²

According to data from the Brazilian registry of HF (BREATHE), ischemic and hypertensive heart diseases were the predominant etiologies, together accounting for approximately 48.9% of HF cases. The registry also showed marked regional differences: hypertensive and ischemic etiologies predominated in the Southeast and South regions, whereas Chagas disease accounted for a substantial proportion of cases in the Midwest and Northeast, underscoring the influence of local epidemiological characteristics on the manifestation of HF.²³

Globally, data from the GBD study demonstrated a significant increase in the prevalence of ischemic heart disease (98.7%) and hypertensive heart disease (137.9%) between 1990 and 2019. In 2019, these conditions were the cause of HF in 33.5% and 41.1% of cases, respectively. In countries with a low sociodemographic index, rheumatic heart disease and streptococcal infections remain important causes of HF, particularly among children and adolescents.^{21,24}

Given Brazil's well-recognized geographic diversity and social inequality, the Rosa dos Ventos multicenter study represents an important national initiative. Its forthcoming findings on the epidemiology of chronic HF are expected to contribute to a better understanding of the condition and the development of more effective strategies.²⁵

2.10. Prognosis

The prognosis of HF is multifactorial and depends on the interplay among demographic characteristics, disease etiology, comorbidities, ejection fraction, and biomarkers.

Advanced age is associated with increased mortality, reflecting a greater burden of comorbidities and reduced physiological reserve.²⁶ Regarding sex, although previous studies have suggested better survival among women, more recent evidence indicates comparable mortality rates between men and women after hospitalization.²⁷

Etiology plays an important prognostic role. Data from the Brazilian BREATHE registry show that Chagas cardiomyopathy is associated with the highest mortality rate (48.04 per 100 patient-years), followed by ischemic (35.2) and nonischemic (27.76) cardiomyopathies.²³

Comorbidities such as diabetes mellitus and renal or hepatic dysfunction are associated with worse outcomes, including increased risks of all-cause mortality, cardiovascular events, and hospitalization.²⁸ In patients with DHF, multiple organ dysfunction is a marker of poor prognosis.²⁹

Ejection fraction also influences outcomes. Both HFrEF and HFpEF are associated with increased morbidity and

mortality, although they differ in clinical characteristics and risk profiles.³⁰ Patients with HF with improved ejection fraction (HFimpEF) tend to have a lower risk of events.³¹

Among biomarkers, BNP has a well-established role in risk stratification. In patients with *de novo* decompensated HFpEF, elevated BNP levels have been associated with up to a 16-fold increased risk of mortality at 12 months.³²

2.11. Morbidity and Mortality in Heart Failure

Despite major therapeutic advances, HF continues to be associated with high mortality.³³ Globally, substantial geographic disparities have been observed in annual mortality rates. Western Europe reports the lowest rates (6.7%), followed by North America (7.9%), whereas Latin America has higher annual mortality (10.1%).³⁴ In contrast, annual mortality in sub-Saharan Africa may reach 34%, reflecting structural barriers and limited access to specialized care.³⁵ Economic disparities between countries have a direct impact on HF outcomes, with higher mortality observed in lower-income nations.³⁶

In Brazil, findings from the 2-phase BREATHE study demonstrated high rates of mortality and readmission. In-hospital mortality was 10.9%, while cumulative mortality at 12 months reached 27.7%. Readmission rates were 24.3% at 90 days and 44.4% at 1 year.²³ These findings underscore the need for more effective strategies to improve HF management and reduce its clinical and societal burden in Brazil.

3. Diagnosis of Heart Failure

3.1. General Principles of Diagnosis: Key Steps

From a practical standpoint, the universal definition of HF proposed in 2013³ and reinforced by its 2026 update⁶ emphasizes the importance of an integrated approach that combines clinical findings, NP levels, when available, and cardiac imaging to establish an accurate diagnosis of HF. Consistent with these principles, Figure 3.1 presents a diagnostic algorithm for HF. The diagnostic process begins with clinical suspicion, based on the presence of risk factors, characteristic signs and symptoms, and abnormalities detected on the electrocardiogram (ECG) and/or chest radiograph. These widely available tests contribute to screening and assist in identifying etiologies and/or comorbidities associated with HF.^{37,38}

The next step is to determine whether there is evidence of increased filling pressures, which may be assessed by measuring NP levels or by identifying objective evidence of pulmonary and/or systemic cardiogenic edema. NPs, primarily BNP and NT-proBNP, are important biomarkers for the diagnosis of HF. These peptides are released in response to cardiac wall stretch and reflect increased cardiac pressure and volume overload. Because BNP measurement has a high negative predictive value, HF can generally be excluded in outpatients with NT-proBNP < 125 pg/mL or BNP < 35 pg/mL, and alternative causes of the patient's symptoms should be investigated (Figure 3.1). Levels above these cutoff values

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increase the likelihood of HF, particularly in the setting of acute dyspnea.³⁹ When NP levels are elevated, the subsequent step is to investigate structural and/or functional cardiac abnormalities that support the diagnosis of HF, most commonly by echocardiography.

When BNP testing is unavailable, or when patients already have objective evidence of congestion, echocardiography may be performed directly to identify structural/functional cardiac abnormalities that support and confirm the diagnosis of HF.

Echocardiography is a safe, widely available imaging modality that provides a comprehensive assessment of cardiac structure and function in patients with suspected HF.⁴⁰ In patients without echocardiographic evidence of compatible structural or functional cardiac abnormalities (Chart 3.1), the diagnosis of HF is unlikely, and alternative causes of the patient's symptoms should be investigated (Figure 3.1). It is important to recognize that these criteria have a high specificity for the diagnosis of HF, approximately 90%. However, in patients with HFpEF who present predominantly with exertional dyspnea, their sensitivity is reduced, at approximately 60%.⁴¹ Therefore,

patients who remain symptomatic in this setting should undergo additional evaluation for HFpEF, as discussed in Chapter 6.2.

Once the diagnosis of HF has been established, the investigation of specific etiologies underlying the different phenotypes according to LVEF should be initiated.

3.2. Investigation of the Etiology of Chronic Heart Failure

Determining the etiology of HF is a critical step in establishing personalized therapeutic strategies, a cornerstone of precision cardiovascular medicine.^{1,42,43} Etiologic investigation should be undertaken as early as possible, ideally at the time of the initial diagnosis. Identifying the underlying cause is essential because, in many cases, etiology-specific treatment can lead to complete reversal of the clinical syndrome. Potentially reversible causes, such as myocarditis, tachycardia-induced cardiomyopathy, and drug-induced cardiotoxicity, exemplify conditions in which appropriate etiologic management may restore cardiac function and substantially improve patient prognosis.^{1,11,42,44,45}

The etiologic evaluation of HF should begin with a systematic approach that integrates family history, personal

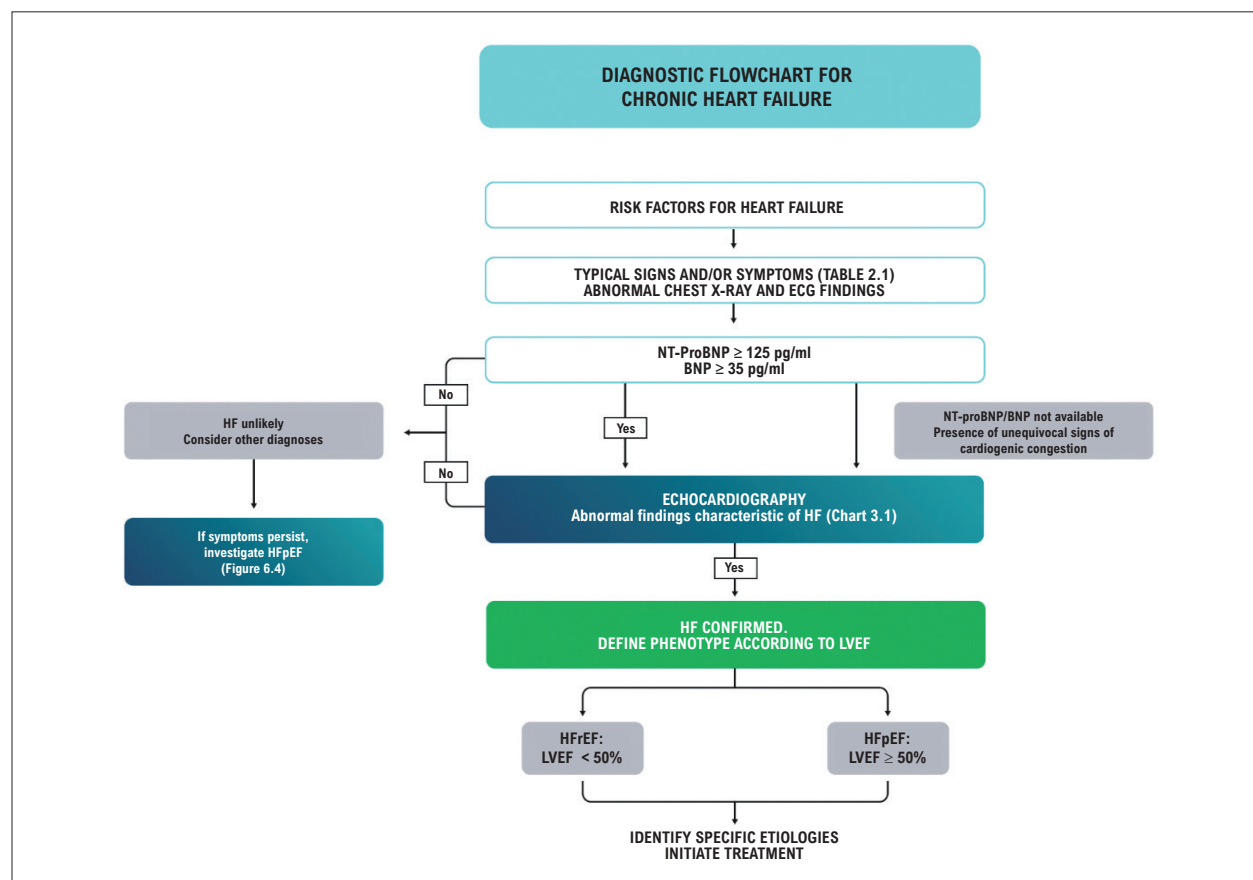


Figure 3.1 – Diagnostic algorithm for chronic heart failure. BNP: B-type natriuretic peptide; ECG: electrocardiogram; HF: heart failure; HFmrEF: heart failure with mildly reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro-B-type natriuretic peptide; X-ray: radiography.

Chart 3.1 – Structural and functional echocardiographic abnormalities that support the diagnosis of heart failure according to left ventricular ejection fraction

Criterion	Heart failure with reduced ejection fraction (HFrEF)	Heart failure with preserved ejection fraction (HFpEF)
Clinical criteria	Symptoms ± signs ¹	Symptoms ± signs ¹
LVEF	LVEF < 50%	LVEF ≥ 50%
Evidence of diastolic dysfunction or increased LV filling pressure	–	HFpEF: Left ventricular mass index ≥ 95 g/m ² (women) or ≥ 115 g/m ² (men); LV relative wall thickness > 0.42; left atrial volume index > 34 mL/m ² ; resting E/e' ratio > 9; pulmonary artery systolic pressure ≥ 35 mmHg; tricuspid regurgitation velocity > 2.8 m/s.

PA: pulmonary artery; EF: ejection fraction; LVEF: left ventricular ejection fraction; HF: heart failure; LV: left ventricle.

medical history, comorbidities, clinical presentation (signs and symptoms), and lifestyle factors. Particular attention should be given to identifying risk factors for the most common causes of HF, including coronary artery disease (CAD; smoking, diabetes, obesity, and dyslipidemia), hypertension, exposure to potentially cardiotoxic substances (eg, alcohol, cocaine, doxorubicin, and anabolic steroids), and infectious diseases, particularly Chagas disease. This evaluation should be combined with initial laboratory testing, ECG, and echocardiography. Comprehensive echocardiography provides valuable information for the identification of the etiology of HF. In particular, myocardial strain imaging has emerged as a useful tool for the early detection and characterization of specific cardiomyopathies in a multimodal approach.^{1,11,42}

Subsequent complementary investigations should be selected in accordance with the initial hypotheses. In most cases, cardiovascular imaging is the preferred next step. Depending on the clinical context and individual patient characteristics, additional investigations may include genetic testing, Holter monitoring, ambulatory blood pressure (BP) monitoring, coronary computed tomography angiography (CCTA), cardiac magnetic resonance imaging (CMR), myocardial scintigraphy, coronary angiography, and invasive hemodynamic assessment.

Common etiologies of HF, such as CAD, systemic arterial hypertension, and valvular heart disease, are addressed in dedicated guidelines for diagnosis and management. Although less prevalent, congenital heart disease should also be considered and managed according to disease-specific recommendations.

The main etiologies of HF are summarized in Figure 3.2.

In addition to the etiologic evaluation of HF, clinicians should maintain a high index of suspicion for conditions that may mimic or coexist with HF, such as anemia, hypothyroidism, and acute or chronic infections. These

comorbidities can not only hinder the correct diagnosis of HF but also contribute substantially to clinical decompensation and persistent symptoms despite optimal treatment of ventricular dysfunction.

3.2.1. Cardiomyopathies as a Cause of Heart Failure

Cardiomyopathies are defined as myocardial disorders in which the heart muscle is structurally and functionally abnormal in the absence of secondary causes, such as CAD, hypertension, valvular heart disease, pericardial disease, and congenital heart disease. In patients with HF in whom these more common etiologies have been excluded, the investigation should proceed toward the identification of specific cardiomyopathies^{46,47} (Figure 3.3).

Cardiomyopathies are classified according to phenotypic subtypes based on the identification of the main morphological and functional characteristics of the myocardium into hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), non-dilated LV cardiomyopathy (NDLVC), arrhythmogenic RV cardiomyopathy (ARVC), and restrictive cardiomyopathy (RCM).^{46,47} In contrast, LV noncompaction is currently regarded as a phenotypic trait, and the term hypertrabeculation is preferred because it may occur in isolation or in association with other phenotypes, such as ventricular dilation or hypertrophy.⁴⁸⁻⁵²

When investigating cardiomyopathies as the cause of HF, multimodality imaging should be used to characterize cardiac morphology, define the phenotypic presentation, and assess myocardial tissue characteristics.

Figure 3.3 summarizes the diagnostic approach to the different cardiomyopathies associated with HF according to the presenting phenotype, based on LVEF and LV wall thickness. The HFrEF phenotypes include DCM, which is characterized by ventricular dilation and systolic dysfunction in the absence of abnormal loading conditions or significant CAD.⁴⁷

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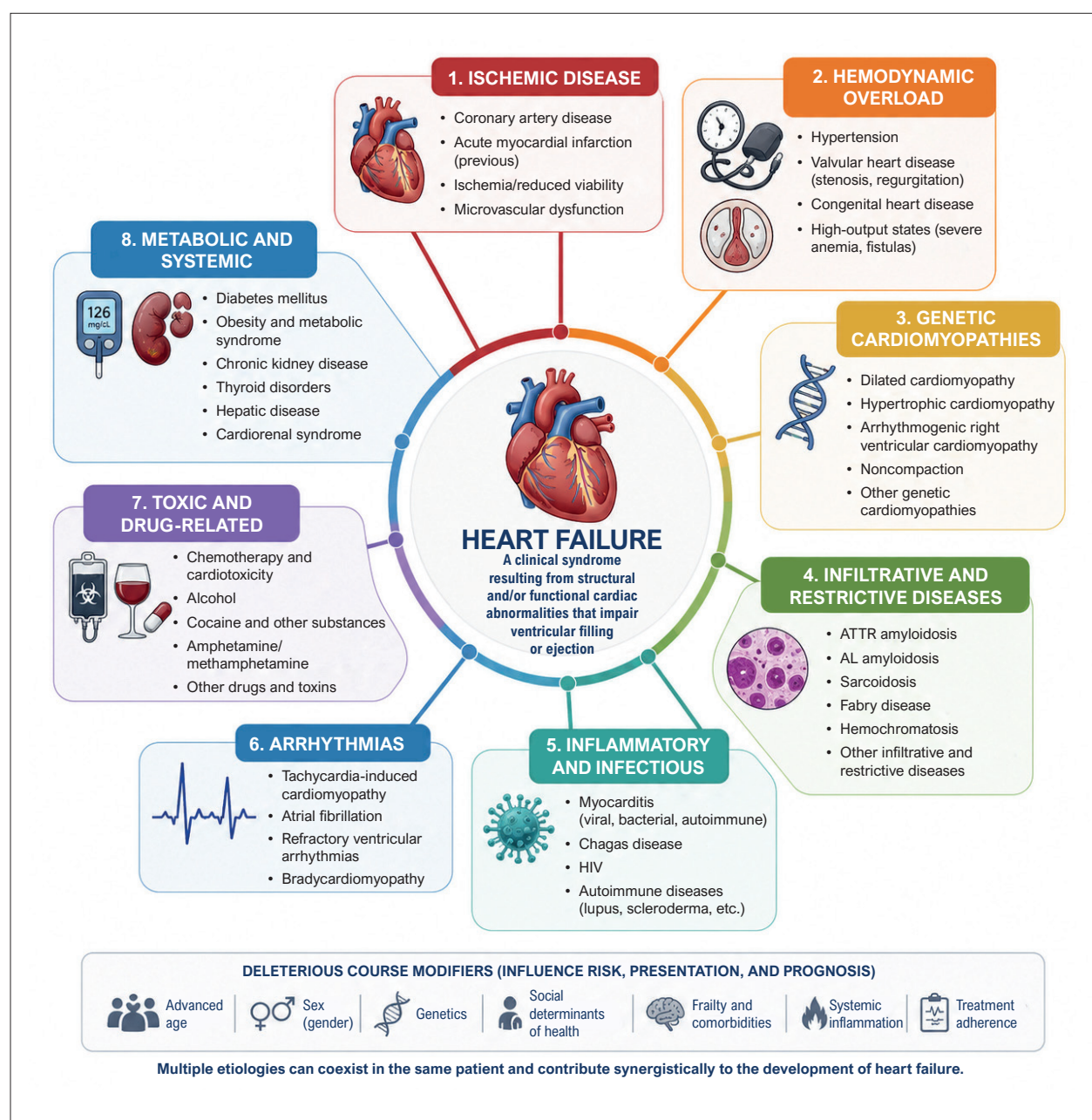


Figure 3.2 – Main etiologies of heart failure. Generated with the assistance of ChatGPT; verified and edited for accuracy by the authors. ATTR: transthyretin amyloidosis; AL: light-chain amyloidosis.

The HFpEF phenotype without increased LV wall thickness includes non-infiltrative RCMs, such as idiopathic RCM, cardiac sarcoidosis, hemochromatosis, and endomyocardial fibrosis. RCM is defined as the presence of restrictive physiology (severe diastolic dysfunction and elevated ventricular filling pressures) in patients with normal or reduced diastolic volumes of one or both ventricles and normal or reduced systolic volumes.⁴⁶

The HFpEF phenotype with increased LV wall thickness includes HCM and infiltrative RCMs, such as cardiac amyloidosis.⁴⁶

HCM is defined as LV wall thickness ≥ 15 mm in adults, or ≥ 13 mm in adults with a first-degree relative affected by HCM, involving 1 or more LV segments that cannot be explained by abnormal loading conditions or increased afterload. In HCM, hypertrophy represents a primary abnormality caused by pathogenic variants in genes encoding sarcomeric proteins. HCM is the most common cardiomyopathy, affecting up to 1 in 250 individuals. Specific considerations regarding its diagnosis and management are available in a recently published guideline.⁵³

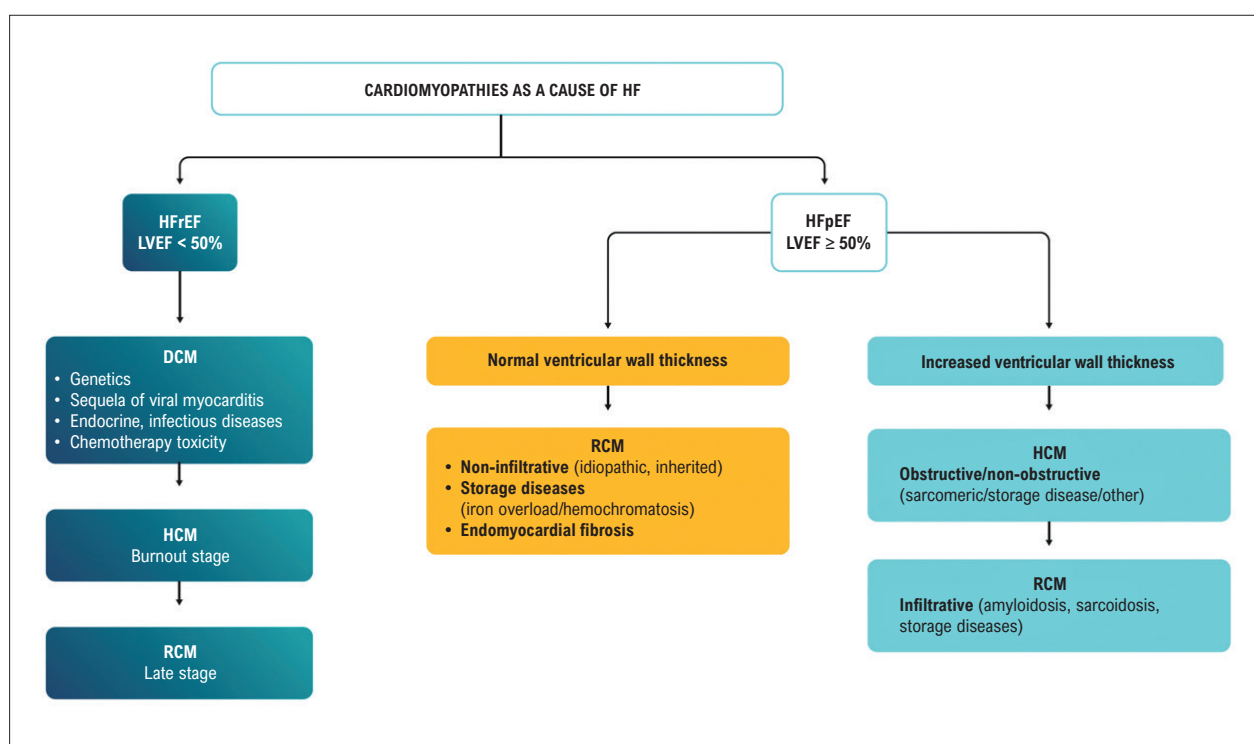


Figure 3.3 – Cardiomyopathies as a cause of heart failure according to the presenting phenotypes. DCM: dilated cardiomyopathy; HCM: hypertrophic cardiomyopathy; HF: heart failure; HFpEF: HF with preserved ejection fraction; HFrEF: HF with reduced ejection fraction; LVEF: left ventricular ejection fraction; RCM: restrictive cardiomyopathy.

In cardiac amyloidosis, increased ventricular wall thickness results from the deposition of misfolded protein fibrils in the myocardial interstitium. The most common form is wild-type transthyretin amyloidosis, although hereditary forms associated with pathogenic variants in the transthyretin gene also occur. Once considered a rare disease, it is currently recognized as the etiology of HFpEF in 10% to 20% of cases. Detailed considerations regarding the diagnosis and treatment of cardiac amyloidosis are available in a recently published position statement.⁴³

3.2.2. Genetic Evaluation in Cardiomyopathies

Genetic evaluation plays a key role in the diagnosis and management of cardiomyopathies and has evolved over the years. The increasing availability of genetic testing has enabled the identification of pathogenic or likely pathogenic monogenic variants, allowing the establishment of a (more precise) molecular diagnosis. This, in turn, facilitates family screening and positively impacts the treatment of these diseases at an early stage.⁵⁴

All cardiomyopathy phenotypes may benefit from genetic evaluation. Although several DNA sequencing approaches are currently available, targeted gene panels remain the most commonly used strategy.⁵⁴ Genetic testing should be considered in all patients with cardiomyopathy, particularly in those who: (1) have a family history of cardiomyopathy or sudden cardiac death (SCD); (2) develop disease

manifestations at an early age (before 40 years); or (3) exhibit abnormalities on complementary diagnostic tests suggestive of cardiomyopathy (Figure 3.4).⁵⁵

In a recent study by Grondin et al., involving a cohort of patients with inherited cardiomyopathies and arrhythmias, a family history of cardiomyopathy and/or SCD was a significant predictor, increasing the yield of genetic testing by approximately 20% compared with patients with a negative family history.⁵⁶ In the same study, positive genetic test results led to changes in the clinical management of probands in 8% of cases.⁵⁶

The genes most frequently associated with the different cardiomyopathy phenotypes are listed in Chart 3.2.⁴⁶

Careful selection of patients with the highest likelihood of harboring a disease-causing genetic variant can improve the yield of genetic testing, which varies according to phenotype, population, and testing methodology. For example, the diagnostic yield of genetic testing in HCM ranges from 26.8% to 70.0%, depending on the study and cohort analyzed.^{57,58} Predictive tools, such as the Mayo Clinic score for HCM and the Madrid score for DCM, aim to increase this yield.^{59,60}

Genetic evaluation should be performed by a geneticist or a cardiologist with expertise in the field, with appropriate pre-test and post-test genetic counseling. Genetic test results should be interpreted within the clinical context of the patient. Table 3.1 summarizes the recommendations for genetic testing in patients with cardiomyopathies.

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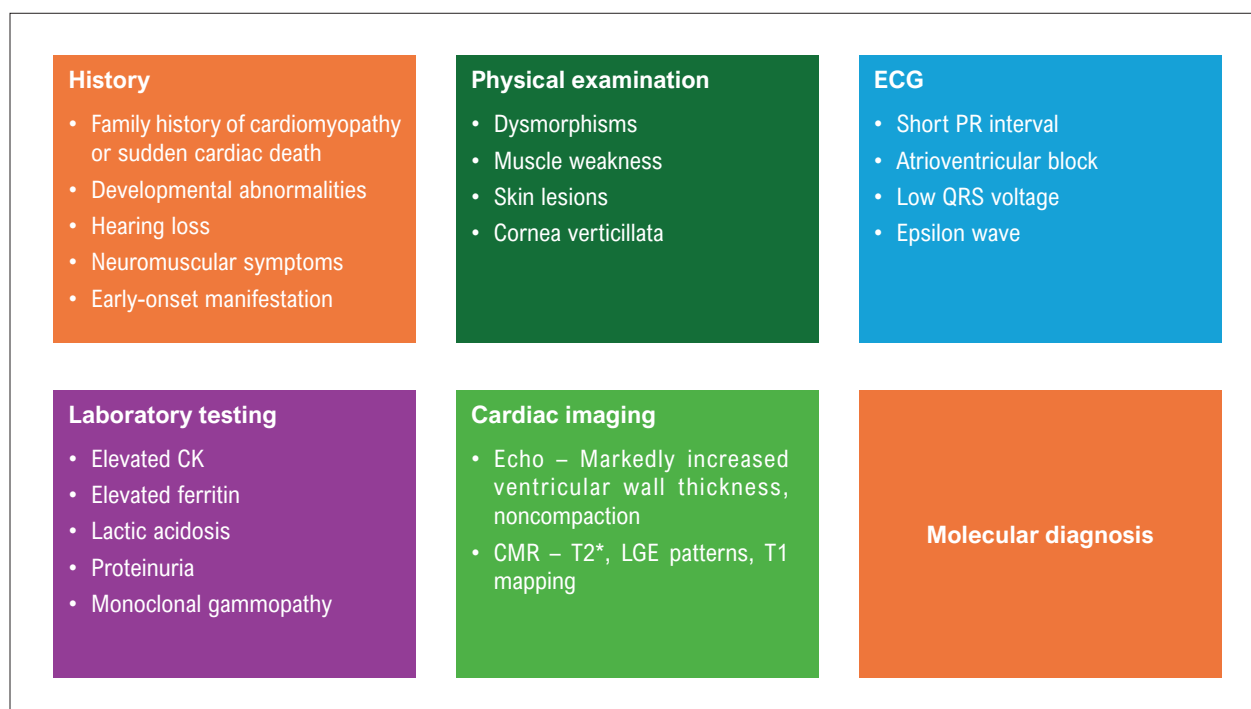


Figure 3.4 – Clinical red flags suggestive of genetic cardiomyopathy. CK: creatine kinase; ECG: electrocardiogram; Echo: echocardiogram; CMR: cardiac magnetic resonance; LGE: late gadolinium enhancement.

Chart 3.2 – Most prevalent genes in cardiomyopathy phenotypes⁵⁶

Cardiomyopathy (CM)	Gene
Hypertrophic CM	MYBPC3, MYH7, TNNT2
Dilated CM	TTN, LMNA, MYH7
Non-dilated left ventricular CM	FLNC, LMNA
Arrhythmogenic right ventricular CM	PKP2, DSC2, DSG2, DSP
Restrictive CM	TTR, TNNI3

Table 3.1 – Recommendations for genetic testing in cardiomyopathies

Recommendation	Strength of recommendation	Certainty of evidence
In probands with a phenotype of a potentially inherited cardiomyopathy, we recommend IN FAVOR OF genetic testing to establish a molecular diagnosis, improve risk stratification, and enable more accurate genetic counseling for family members.	STRONG	MODERATE
In patients with cardiomyopathy of unknown etiology, we recommend IN FAVOR OF genetic testing when abnormalities identified on complementary diagnostic tests are suggestive of an underlying genetic disorder.	STRONG	LOW
In family members of probands in whom a pathogenic or likely pathogenic variant has been identified in association with a cardiomyopathy phenotype, we recommend IN FAVOR OF genetic evaluation to establish a molecular diagnosis and enable early clinical follow-up.	STRONG	MODERATE

4. Complementary Tests

4.1. Laboratory Testing

In the initial evaluation of patients with signs and symptoms suggestive of HF, the following complementary laboratory tests are recommended to assess the presence and severity of end-organ damage and to detect comorbidities or factors contributing to clinical deterioration: complete blood count; urinalysis; serum electrolytes (sodium, potassium, calcium, and magnesium); assessment of renal function (urea and creatinine); fasting plasma glucose and glycated hemoglobin (HbA1c); lipid profile; thyroid function tests (free thyroxine [free T4] and thyroid-stimulating hormone [TSH]); liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma-glutamyl transferase [GGT], and bilirubin); and iron studies.

Serial laboratory testing may also be used to monitor safety-related variables during HF treatment, including renal function and electrolyte concentrations.

4.2. Noninvasive Imaging

4.2.1. Resting Electrocardiogram

A 12-lead ECG is part of the routine initial evaluation of all patients with HF and provides information on cardiac rhythm, heart rate (HR), chamber enlargement, and QRS morphology and duration. Many of these findings may suggest a specific etiology or serve as important prognostic markers. For example, QRS duration is a key parameter for identifying candidates for cardiac resynchronization therapy (CRT).⁶¹

4.2.2. Chest Radiography

Chest radiography is a simple, rapid, and widely available imaging modality that is recommended for patients with signs and symptoms of HF. It allows assessment of heart size and the presence of pulmonary congestion. In patients with new-onset DHF, patients with recent-onset HF, and those with HFpEF, the cardiac silhouette may appear normal.

Chest radiography is also useful for identifying alternative causes of similar clinical presentations, such as pulmonary diseases. However, a normal chest radiograph does not exclude HF, as the sensitivity and specificity of this modality are limited.⁶²

4.2.3. Echocardiography

Transthoracic echocardiography (TTE) is a safe, widely available imaging modality that provides a comprehensive assessment of cardiac structure and function in patients with suspected HF. In addition to evaluating LVEF, ventricular wall thickness, valve structure, central vessels, and the pericardium, TTE provides essential information on diastolic function through parameters such as the E/e' ratio, left atrial (LA) volume, and estimated pulmonary artery pressure (PAP), all of which are important for assessing diastolic function and identifying patterns of cardiac remodeling.

Beyond structural assessment, TTE also provides valuable

hemodynamic information by evaluating LV systolic and diastolic function and estimating filling pressures. Doppler techniques (pulsed-wave, continuous-wave, and tissue Doppler imaging) provide essential information for the management of HF, as intravascular volume status is a major determinant of HF signs and symptoms. Pulmonary artery systolic pressure (PASP) can be estimated from the systolic pressure gradient between the right atrium and RV, derived from continuous-wave Doppler assessment of tricuspid regurgitation (TR), together with inferior vena cava (IVC) inspiratory collapsibility. Both RV contractile function and PASP are important prognostic markers in HF. LVEF, calculated using Simpson's method, has broad clinical applicability because it allows estimation of the severity of LV dysfunction (mild, moderate, or severe). In HFpEF, given that the ejection fraction is preserved, it is necessary to use diagnostic scores that incorporate echocardiographic findings.⁶³

Assessment of myocardial deformation using global longitudinal strain (GLS) has been increasingly adopted, particularly for the detection of subclinical ventricular dysfunction. This marker may be particularly valuable in selected populations, especially in patients receiving cardiotoxic chemotherapy and those with cardiomyopathies. Because GLS is not universally available and remains subject to technical variability, its routine use is not currently recommended.^{64,65}

Routine serial TTE is not recommended. Repeat examinations should be performed only when there are significant changes in clinical status or after interventional procedures, such as device implantation or myocardial revascularization. In patients with HF who experience meaningful clinical changes or who have received optimal GDMT, particularly when invasive procedures or device therapy are being considered, reassessment of LVEF, the degree of cardiac remodeling, and valvular function is essential to guide treatment decision-making.

4.2.3.1. Transesophageal echocardiography

Transesophageal echocardiography (TEE) should be reserved for selected clinical scenarios, such as valvular heart diseases requiring more detailed anatomical assessment. In carefully selected patients with HF who are candidates for transcatheter edge-to-edge mitral valve repair (MitraClip), TEE is indispensable for comprehensive mitral valve evaluation.⁶⁶

In addition, TEE should be performed in patients being considered for catheter ablation of atrial fibrillation (AF) to exclude the presence of thrombus in the LA appendage.

Table 4.1 summarizes the recommendations for the use of complementary tests in patients with HF.

4.2.4. Cardiac Magnetic Resonance Imaging

CMR has become the reference standard for morphological and functional assessment of the heart in contemporary clinical practice.⁶⁷ In addition to providing quantification of cardiac function, CMR offers unique capabilities for myocardial tissue characterization. Through late gadolinium enhancement (LGE) imaging, it can distinguish ischemic from nonischemic

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Table 4.1 – Recommendations for the use of complementary tests in the evaluation of patients with heart failure

Recommendation	Strength of recommendation	Certainty of evidence
In patients with signs and symptoms suggestive of HF, we recommend IN FAVOR OF obtaining a complete blood count, urinalysis, serum electrolytes, assessment of renal function, fasting plasma glucose, glycated hemoglobin, lipid profile, thyroid function tests, liver function tests, and iron studies.	STRONG	LOW
In patients with signs and symptoms suggestive of HF, we recommend IN FAVOR OF serial laboratory monitoring of renal function and serum electrolytes throughout treatment.	STRONG	HIGH
In patients with signs and symptoms suggestive of HF, we recommend IN FAVOR OF obtaining a resting 12-lead electrocardiogram.	STRONG	MODERATE
In patients with signs and symptoms suggestive of HF, we recommend IN FAVOR OF obtaining a chest radiograph.	STRONG	LOW
In patients with suspected HF, we recommend IN FAVOR OF performing transthoracic echocardiography.	STRONG	HIGH

HF: heart failure.

etiologies of cardiac dysfunction.^{68,69} The extent of transmural LGE also has important clinical value, as it predicts the likelihood of functional recovery after revascularization. Myocardial segments with < 50% transmural extent of hyperenhancement have a greater likelihood of recovering contractile function after coronary revascularization.⁷⁰ Stress CMR provides excellent diagnostic accuracy for the detection of myocardial ischemia.⁷¹⁻⁷⁴ In addition, LGE imaging may be used to assess myocardial viability in patients with ischemic heart disease when this information is necessary to guide clinical decision-making.

CMR is particularly valuable in the evaluation of specific cardiomyopathies, including amyloidosis, sarcoidosis, Fabry disease, and hemochromatosis. Early identification of these conditions is enhanced by the use of T1, T2, and T2* mapping, which improve diagnostic sensitivity.⁷⁵⁻⁸⁰ The high spatial resolution of CMR also enables accurate characterization of apical aneurysms in patients with chronic Chagas cardiomyopathy.⁸¹⁻⁸³ Contemporary CMR protocols routinely include cine imaging for assessment of global and regional ventricular function, mapping for tissue characterization, and post-contrast LGE imaging for the detection of fibrosis. Although CMR has historically been limited in patients with cardiac implantable electronic devices, technological

advances – including the adoption of dedicated imaging protocols and the availability of MR-conditional devices – have made the examination feasible and safe for most of these patients.⁸⁴ Finally, concerns regarding the risk of nephrogenic systemic fibrosis in patients with renal dysfunction have led to the development of gadolinium-based contrast agents with improved safety profiles.⁸⁵

Table 4.2 summarizes the recommendations for the use of CMR.

4.2.5. Nuclear Medicine: Single-Photon Emission Computed Tomography and Positron Emission Tomography

Single-photon emission computed tomography (SPECT) myocardial perfusion imaging and positron emission tomography (PET) are well-established imaging modalities in the evaluation of patients with HF, particularly for the assessment of ischemia, myocardial viability, cardiac sarcoidosis, and cardiac amyloidosis. Myocardial perfusion SPECT, using radiotracers such as technetium-99m (99mTc)-labeled sestamibi, remains widely used for the detection of myocardial ischemia and the assessment of myocardial viability, especially in patients with HF and suspected CAD.⁸⁶ Areas of hypoperfusion with preserved wall motion are

Table 4.2 – Recommendations for the use of cardiac magnetic resonance imaging in patients with heart failure

Recommendation	Strength of recommendation	Certainty of evidence
In patients with signs and symptoms suggestive of heart failure, we recommend IN FAVOR OF cardiac magnetic resonance imaging for anatomical and functional assessment when echocardiography is inconclusive.	STRONG	HIGH
We recommend IN FAVOR OF cardiac magnetic resonance imaging with myocardial tissue characterization and late gadolinium enhancement imaging for the differential diagnosis and etiologic evaluation of cardiomyopathies.	STRONG	HIGH

suggestive of ischemia, whereas absent perfusion associated with regional wall motion abnormalities indicates necrosis or irreversible fibrosis. Technetium-99m pyrophosphate (99mTc-PYP) scintigraphy has high diagnostic accuracy for transthyretin cardiac amyloidosis (ATTR-CA), enabling a noninvasive diagnosis when interpreted in conjunction with the exclusion of monoclonal gammopathy.⁸⁷ Fluorine-18 fluorodeoxyglucose (18F-FDG) PET provides quantitative assessment of myocardial glucose metabolism and has demonstrated high accuracy for the identification of viable myocardium.^{88,89} Its ability to detect active myocardial inflammation makes it particularly valuable in patients with suspected cardiac sarcoidosis, complementing the information provided by CMR.⁹⁰ It is also useful for establishing the diagnosis and monitoring the response to immunosuppressive therapy.^{91,92}

Table 4.3 summarizes the recommendations for the use of scintigraphic examinations.

4.2.6. Coronary Computed Tomography Angiography

CCTA is a noninvasive diagnostic imaging modality that has become increasingly important in the evaluation of patients with HF. Its ability to exclude significant CAD is particularly valuable in patients with a low to intermediate pretest probability of CAD, providing an alternative to invasive coronary angiography.

Studies have demonstrated that CCTA has high diagnostic accuracy and may reduce the need for unnecessary invasive procedures.^{93,94} Beyond its role in the detection of CAD,

CCTA has emerged as an important tool for planning percutaneous structural heart interventions in patients with HF.⁹⁵ These include transcatheter aortic valve implantation (TAVI), mitral valve interventions, and other percutaneous structural interventions such as LA appendage occlusion and patent foramen ovale closure. In the preoperative assessment of patients undergoing valvular heart surgery, CCTA has been increasingly used to exclude CAD in individuals with a low to intermediate risk, potentially obviating the need for invasive coronary angiography.^{96,97} The limitations of CCTA should also be considered, including exposure to ionizing radiation and the use of iodinated contrast media, especially in patients with impaired renal function. Therefore, the decision to perform CCTA should be individualized, weighing its diagnostic benefits against potential contraindications in each patient.

Table 4.4 summarizes the recommendations for the use of CCTA.

4.3. Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing (CPET), also known as ergospirometry, provides an objective assessment of functional capacity by measuring peak oxygen consumption (peak $\dot{V}O_2$). In addition, CPET evaluates other important prognostic variables, including the minute ventilation/carbon dioxide production ($\dot{V}_E/\dot{V}CO_2$) slope and the presence of exercise oscillatory ventilation.⁹⁸

CPET is considered the gold standard for the assessment of functional capacity and has well-established prognostic value in patients with HF. It is recommended as part of

Table 4.3 – Recommendations for the use of SPECT and PET in patients with heart failure

Recommendation	Strength of recommendation	Certainty of evidence
In patients with HF and suspected coronary artery disease, we recommend IN FAVOR OF myocardial perfusion SPECT for the assessment of myocardial ischemia.	STRONG	MODERATE
In patients with HF, left ventricular dysfunction, and established coronary artery disease, we recommend IN FAVOR OF myocardial perfusion SPECT or 18F-FDG PET as an option for the assessment of myocardial viability.	STRONG	MODERATE
We recommend IN FAVOR OF 99mTc-PYP SPECT for the noninvasive diagnosis of transthyretin cardiac amyloidosis, after exclusion of monoclonal gammopathy.	STRONG	HIGH

HF: heart failure; SPECT: single-photon emission computed tomography; PET: positron emission tomography; 18F-FDG: fluorine-18 fluorodeoxyglucose; 99mTc-PYP: technetium-99m pyrophosphate.

Table 4.4 – Recommendations for the use of coronary computed tomography angiography

Recommendation	Strength of recommendation	Certainty of evidence
In patients with a low to intermediate pretest probability of coronary artery disease or those with inconclusive results on other noninvasive tests for ischemia, we recommend IN FAVOR OF coronary computed tomography angiography to exclude significant coronary artery disease as the cause of heart failure.	STRONG	HIGH

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the evaluation of patients who are candidates for heart transplant.⁹⁹ In addition, CPET should be considered in clinically stable patients with HF for the assessment of functional capacity and for the differential diagnosis of the cause of dyspnea (eg, anxiety, pulmonary disease, and skeletal muscle dysfunction).¹⁰⁰

Table 4.5 summarizes the recommendations for the use of CPET.

4.4. Biomarkers

4.4.1. Natriuretic Peptides

NPs are the reference standard biomarkers for HF. Measurement of BNP or NT-proBNP may be useful in patients presenting with dyspnea when the diagnosis of HF remains uncertain and may also serve as a screening tool

in the primary care setting.^{101,102} In outpatients, BNP levels < 35 pg/mL or NT-proBNP levels < 125 pg/mL make the diagnosis of HF unlikely.¹⁰¹ Values above these thresholds should prompt further evaluation with echocardiography to confirm the diagnosis when clinical assessment alone is inconclusive (Chart 4.1).

In addition to their diagnostic utility, NPs provide important prognostic information, complementing the findings of the clinical evaluation and routine laboratory tests.¹⁰¹ After dose titration, NP concentrations are expected to decline in response to treatment. Failure of NP levels to decrease, or a subsequent increase, is associated with poor prognosis.¹⁰³ NP measurements may therefore be useful when the clinical response to therapy remains uncertain. In patients receiving sacubitril-valsartan, NT-proBNP is the preferred biomarker for serial monitoring because sacubitril inhibits BNP degradation, potentially causing a modest

Table 4.5 – Recommendations for the use of cardiopulmonary exercise testing

Recommendation	Strength of recommendation	Certainty of evidence
In patients with advanced HF, we recommend IN FAVOR OF CPET to assess eligibility for advanced therapies, such as heart transplant or ventricular assist devices.	STRONG	MODERATE
In outpatients with HF, we recommend IN FAVOR OF CPET for an objective assessment of functional capacity.	STRONG	MODERATE
In outpatients with symptoms suggestive of HF, we recommend IN FAVOR OF CPET for the differential diagnosis of the underlying cause of dyspnea.	WEAK	MODERATE

HF: heart failure; CPET: cardiopulmonary exercise testing.

Chart 4.1 – Natriuretic peptide cutoff values for the diagnosis of heart failure

Biomarker	HF unlikely (pg/mL)	HF possible (pg/mL)	HF very likely (pg/mL)
Emergency patient			
BNP	< 100	100–400	> 400
NT-proBNP			
<50 years	< 300	300–449	≥ 450
50–75 years	< 300	300–899	≥ 900
>75 years	< 300	300–1.799	≥ 1.800
Outpatient			
BNP	< 35	-----	-----
NT-proBNP			
<50 years	< 125	---	≥ 125
50–75 years	< 125	125–249	≥ 250
>75 years	< 125	125–499	≥ 500

HF: heart failure; BNP: B-type natriuretic peptide; NT-proBNP: N-terminal pro-B-type natriuretic peptide.

increase in BNP concentrations during the early phase of treatment. The magnitude of this effect, however, may vary according to the assay used.¹⁰⁴ Whether NP-guided therapy targeting specific biomarker thresholds improves clinical outcomes remains controversial, with studies reporting conflicting results.¹⁰⁵

It is also important to recognize clinical factors that influence NP concentrations. Elevated NP levels may occur in the setting of advanced age, renal dysfunction, AF, pulmonary hypertension, and treatment with neprilysin inhibitors (sacubitril-valsartan), which affect BNP concentrations but not NT-proBNP.¹⁰⁴ Conversely, obesity is associated with lower NP levels.¹⁰⁵

More recently, NPs have also demonstrated prognostic value in asymptomatic individuals with risk factors for HF, identifying the so-called heart stress and potentially predicting the incidence of HF.¹⁰⁶

4.4.2. Other Biomarkers

Additional biomarkers that are not routinely used in clinical practice may provide incremental prognostic information. Measurements of myocardial injury biomarkers, such as cardiac troponin T and I (including high-sensitivity troponin), as well as biomarkers of inflammation and fibrosis, such as galectin-3 and soluble suppression of tumorigenicity 2 (sST2), may offer additional prognostic information.¹⁰⁷⁻¹⁰⁹ Growth differentiation factor-15 (GDF-15), a biomarker of inflammation and oxidative stress, has also demonstrated prognostic value.¹¹⁰ However, there is insufficient evidence to show that the use of these biomarkers improves clinical outcomes. Therefore, current evidence does not support their routine use in the management of HF.

Table 4.6 summarizes the recommendations for the use of NP measurements in the setting of HF.

5. Prevention of Heart Failure: Management in Stages A and B

HF is currently understood as a pathophysiological continuum rather than an isolated event. Early intervention is crucial in its initial stages to modify the disease trajectory and improve long-term outcomes.

5.1. Stage A: Primary Prevention of HF – Identification and Management of Risk Factors

In Stage A, the primary goal is to prevent the development of structural or functional heart disease. This involves identifying and rigorously controlling cardiovascular risk factors. For traditional risk factors such as hypertension and diabetes mellitus, consultation of the condition-specific guidelines is recommended for detailed management.

Risk Factors and Prevention Strategies:

- **Hypertension:** Adequate blood pressure control is the most effective measure for preventing HF. The target should be individualized, although values below 130/80 mmHg are generally recommended.
- **Diabetes Mellitus (DM):** Intensive glycemic management, particularly with sodium–glucose cotransporter 2 inhibitors (SGLT2i), the glucagon-like peptide-1 receptor agonist semaglutide (GLP-1 RA), and the dual glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1 receptor agonist tirzepatide (GIP/GLP-1 RA), has been shown to reduce the risk of HF hospitalization and major cardiovascular events in patients with type 2 DM. These benefits occur regardless of the presence of established cardiovascular disease or prior HF because these drugs act not only through glycemic control but also through direct cardioprotective mechanisms.
- **Dyslipidemia:** Control of cholesterol levels, particularly LDL-C, with statins is essential for preventing atherosclerotic disease and, consequently, HF of ischemic etiology.

Table 4.6 – Recommendations for the use of natriuretic peptide measurements

Recommendation	Strength of recommendation	Certainty of evidence
In patients with symptoms suggestive of HF, we recommend IN FAVOR OF the measurement of BNP or NT-proBNP when diagnostic uncertainty persists after the initial clinical evaluation.	STRONG	HIGH
In patients with HF, we recommend IN FAVOR OF the measurement of BNP or NT-proBNP for prognostic stratification.	STRONG	HIGH
In patients with HF, we recommend IN FAVOR OF serial measurements of BNP or NT-proBNP, in conjunction with physical examination, to reassess prognosis after treatment initiation.	STRONG	MODERATE
In asymptomatic individuals with risk factors for HF, the measurement of BNP or NT-proBNP might be considered for risk stratification.	WEAK	MODERATE

HF: heart failure; BNP: B-type natriuretic peptide; NT-proBNP: N-terminal pro-B-type natriuretic peptide.

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- **Obesity:** Obesity is an independent risk factor and a major driver of HF development, particularly HF with preserved ejection fraction (HFpEF). The “adipokine hypothesis” postulates that dysfunctional adipose tissue releases proinflammatory and profibrotic adipokines, leading to myocardial changes, endothelial dysfunction, vascular stiffness, and pulmonary hypertension. Clinically significant weight loss (≥ 10 –15%) may reverse adverse cardiac remodeling and improve cardiac function. In addition to promoting weight loss, drugs such as GLP-1 RAs and dual GLP-1/GIP receptor agonists have been shown to reduce the risk of cardiovascular events and improve outcomes in patients with obesity and HFpEF by acting on the underlying pathophysiology of the disease. Early intervention for obesity is therefore an effective strategy for HF prevention.¹¹¹
- **Smoking:** Smoking cessation is one of the most cost-effective interventions for reducing cardiovascular risk, including the risk of HF.
- **Excessive alcohol consumption:** Abstinence from or moderation of alcohol consumption is crucial for preventing alcoholic cardiomyopathy.
- **Chemotherapy-related cardiotoxicity:** Patients undergoing cancer treatment with cardiotoxic agents (e.g., anthracyclines and trastuzumab) require rigorous cardiac monitoring and cardioprotective strategies. For detailed management, consultation of the Brazilian Cardio-Oncology Guideline is recommended.
- **Anabolic-androgenic steroids (AAS):** The use of AAS, even at doses considered “moderate” or for limited periods, is associated with a significant risk of cardiomyopathy, ventricular dysfunction, and arrhythmias. Discontinuation is essential for the recovery of cardiac function, although persistent

damage may occur. Awareness of the associated risks and prevention of use are essential.⁴⁵

- **Valvular heart disease:** Early and appropriate treatment of valvular heart disease, such as aortic stenosis and mitral regurgitation, may prevent the development of cardiac overload and HF.
- **Coronary artery disease (CAD):** Prevention and treatment of CAD, including revascularization when indicated, are crucial for preventing HF of ischemic etiology.

Table 5.1 summarizes the recommendations for HF prevention in Stage A

5.2. Stage B: Prevention of HF Progression–Management of Asymptomatic Patients with Structural Heart Disease

This stage represents a critical point for intervention because disease progression can be modified with appropriate treatment. Early identification of asymptomatic left ventricular dysfunction (LVD), significant valvular heart disease, or structural abnormalities of various etiologies—including genetic, inflammatory, ischemic, and toxic etiologies, such as those induced by chemotherapy or anabolic-androgenic steroid use—is essential.

For patients with a history of acute myocardial infarction (AMI) and a left ventricular ejection fraction (LVEF) $\leq 40\%$, the therapeutic approach aims to reduce HF hospitalizations and mortality. Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), as well as beta-blockers, are recommended in this group. Additionally, mineralocorticoid receptor antagonists (MRAs), such as eplerenone or spironolactone, are indicated for the same purpose in post-MI patients with an LVEF $\leq 40\%$ and signs of HF or diabetes.

For patients with reduced LVEF ($< 50\%$) due to other, nonischemic etiologies or with significant left ventricular

Table 5.1 – Recommendations for HF Prevention in Stage A

Recommendation	Strength of Recommendation	Certainty of Evidence
We recommend IN FAVOR OF rigorous control of hypertension, diabetes mellitus, and dyslipidemia to prevent the development of structural and functional heart disease	STRONG	HIGH
We recommend IN FAVOR OF counseling on a healthy lifestyle, including a balanced diet, regular physical activity, and smoking cessation, to reduce the risk of HF	STRONG	HIGH
In patients with type 2 DM, we recommend IN FAVOR OF the use of SGLT2i, a GLP-1 RA (semaglutide), or a dual GIP/GLP-1 RA (tirzepatide) to reduce the risk of HF hospitalization and major cardiovascular events.	STRONG	HIGH
We recommend IN FAVOR OF the assessment and management of chemotherapy-related cardiotoxicity in accordance with the Brazilian Cardio-Oncology Guideline	STRONG	MODERATE

remodeling, the use of ACEIs or ARBs, as well as beta-blockers, should be considered to prevent disease progression and the development of symptoms.¹¹²

For patients with significant valvular heart disease, surgical or percutaneous treatment should follow the condition-specific guidelines to prevent the onset or progression of HF.

For asymptomatic patients with nonischemic dilated cardiomyopathy (NIDCM), treatment with ACEIs/ARBs and beta-blockers is recommended to prevent the progression of ventricular dysfunction and the onset of symptoms.

In the Brazilian context, Chagas heart disease is a relevant etiology at this stage and is characterized by electrocardiographic abnormalities, such as right bundle branch block or left anterior fascicular block, and/or echocardiographic abnormalities, even in the absence of HF symptoms. Although antiparasitic treatment is essential in the acute and early chronic phases, its effectiveness in reversing or preventing the progression of ventricular dysfunction in patients with established Chagas heart disease (Stage B or C) remains a matter of debate. Therefore, the main focus remains on disease-modifying HF therapy, such as ACEIs/ARBs and beta-blockers, for the management of ventricular dysfunction.¹¹³

Table 5.2 summarizes the recommendations for HF prevention in Stage B

Table 5.2 – Pharmacological Recommendations for HF Prevention in Stage B

Recommendation	Strength of Recommendation	Certainty of Evidence
We recommend IN FAVOR OF the use of an ACEI or ARB in cases of intolerance in patients with LVEF $\leq 40\%$ to reduce HF hospitalization and death	STRONG	HIGH
We recommend IN FAVOR OF beta Beta-blocker therapy in patients with LVEF $< 50\%$ to reduce HF hospitalization or death	STRONG	MODERATE
We recommend IN FAVOR OF eplerenone Eplerenone in post-MI patients with LVEF $\leq 40\%$ and signs of HF or diabetes to reduce HF hospitalization and death	STRONG	MODERATE

6. Chronic Heart Failure

6.1. Heart Failure with Reduced Ejection Fraction

HFrEF (LVEF $< 50\%$) is characterized by LV systolic dysfunction and progressive cardiac remodeling driven by neurohormonal activation, inflammation, and myocardial fibrosis. It is a clinically heterogeneous syndrome associated with substantial morbidity and mortality, in which phenotypic stratification and early intervention are determinants of prognosis. This chapter summarizes the pathophysiological principles and evidence base supporting contemporary management, with an emphasis on disease-modifying therapies and their rapid, safe, and individualized implementation.

6.1.1. Pathophysiology and Mechanisms of HFrEF Progression

In HFrEF, decompensated or chronic myocardial injury reduces systolic function, triggers inflammation, and is associated with cell death and progressive replacement by fibrosis, leading to cardiac remodeling with LV chamber dilation. These structural changes produce volume overload, pulmonary congestion, and, in advanced stages, systemic congestion, culminating in reduced cardiac output. The decline in cardiac output and BP compromises tissue perfusion, creating a state of hypoperfusion that is perceived by the body as a threat to homeostasis and initiates sustained neurohormonal activation.

In this process, the kidneys serve as an early responder. Arterial underfilling and reduced effective circulating volume stimulate juxtaglomerular cells to release renin, which converts angiotensinogen into angiotensin I, subsequently transformed into angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II induces peripheral vasoconstriction and stimulates aldosterone secretion, increasing sodium and water reabsorption, expanding intravascular volume, and promoting myocardial fibrosis and inflammatory activation in HF. Although initially beneficial, chronic activation of the renin–angiotensin–aldosterone system (RAAS) becomes deleterious, as it exacerbates congestion, contributes to inflammation, and induces myocardial fibrosis, perpetuating cardiac remodeling.

Conversely, myocardial stretch caused by pressure or volume overload stimulates the release of BNP and NT-proBNP, which function as compensatory mechanisms. These hormones promote vasodilation, increased urine output, and antihypertrophic and anti-inflammatory effects while antagonizing the RAAS and the sympathetic nervous system, thereby contributing to alleviating symptoms and attenuating cardiac remodeling. Sacubitril-valsartan enhances these effects by inhibiting neprilysin, the enzyme responsible for the premature degradation of peptides, thereby prolonging their action and improving both symptoms and prognosis.

Hypotension and hypoperfusion also activate the sympathetic nervous system through receptors in the carotid sinus and aortic arch. This activation increases sympathetic tone and stimulates the release of catecholamines, particularly norepinephrine, which initially exerts positive chronotropic and inotropic effects while inducing peripheral

vasoconstriction to preserve perfusion of vital organs. However, chronic catecholamine exposure results in beta-adrenergic receptor desensitization, progressive loss of contractile reserve, increased risk of arrhythmias, cell death, hypertrophy, and fibrosis, ultimately worsening cardiac function. In this setting, beta-blockers play a key role by reducing the sustained deleterious effects of catecholamines on the myocardium. Although they may initially reduce HR and contractility, long-term therapy improves ventricular function, reduces cardiac remodeling, and increases survival.

Aldosterone plays a pivotal physiological role in regulating sodium, potassium, and water homeostasis and also modulates both physiological and pathological processes in the cardiovascular system. Excess aldosterone contributes to endothelial dysfunction, inflammatory activation, and tissue injury. In HF, chronic RAAS activation leads to persistent aldosterone excess, resulting in sustained hemodynamic overload and neurohormonal activation that promote pathological ventricular remodeling characterized by LV hypertrophy and myocardial fibrosis. Under these conditions, aldosterone exerts key deleterious effects that substantially contribute to disease progression and increase the risk of worsening HF.¹¹⁴

Although the precise mechanisms remain incompletely understood, sodium–glucose cotransporter 2 (SGLT2) inhibitors are thought to confer cardiovascular benefits through enhanced natriuresis, anti-inflammatory effects, metabolic control, attenuation of sympathetic activation, reduction of oxidative stress, and subsequent prevention of pathological cardiac remodeling.^{115,116}

Understanding these pathophysiological mechanisms is essential for understanding the progression of HFrEF, assessing prognosis, and guiding individualized, targeted therapeutic strategies that address the complex structural, cellular, hemodynamic, and neurohormonal abnormalities underlying the syndrome.

6.1.2. Treatment of HFrEF

The management of heart failure with reduced ejection fraction (HFrEF) has been transformed by therapeutic advances that have robustly demonstrated the ability to modify the prognosis of the syndrome, reduce mortality and hospitalizations, and significantly improve patients' quality of life. To optimize the implementation of this evidence and guide clinical decision-making, this Guideline adopts the concept of Guideline-Directed Therapy (GDT), which synergistically integrates pharmacological treatment with structural interventions or device-based therapies.

This comprehensive approach consists of three components:

1. **Foundational Medical Therapy (FMT):** This pillar forms the basis of pharmacological treatment for HFrEF and encompasses the drug classes whose efficacy in reducing mortality and modifying the natural history of the disease is well established and supported by robust evidence. As detailed in this chapter, FMT includes renin–angiotensin system inhibitors–angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), or angiotensin receptor–

neprilysin inhibitors (ARNIs)–beta-blockers (BBs), mineralocorticoid receptor antagonists (MRAs), and sodium–glucose cotransporter 2 inhibitors (SGLT2i). These are essential neurohormonal and metabolic blockade therapies indicated for all eligible patients with HFrEF, with the aim of directly improving prognosis.

2. **Additional Medical Therapy (AMT):** This component comprises complementary therapeutic options individually indicated to improve symptoms, reduce hospitalizations, and manage specific phenotypes once FMT has been optimized. The selection of AMT is guided by the patient's clinical course, associated comorbidities, and trends in laboratory parameters.
3. **Guideline-Directed Interventional Therapy (GDIT):** This component encompasses structural interventions and device implantation that provide mechanical support, resynchronization, or correction of valvular heart disease. GDIT is indicated according to specific criteria related to disease severity and persistence of symptoms after optimization of FMT and AMT.

The integration of these concepts is summarized in the strategic equation for clinical management illustrated in Figure 6.1.

This framework is intended to facilitate the implementation of the recommendations, emphasizing that successful treatment of HFrEF depends on implementation in the appropriate sequence and on efforts to optimize doses and interventions across all therapeutic domains. By adopting GDT, patients receive the appropriate treatment at the appropriate stage of their therapeutic journey, aligning the best scientific evidence with their individual needs and, crucially, positively affecting survival.

6.1.3. Foundational Medical Therapy

6.1.3.1. Angiotensin-Converting Enzyme Inhibitors

ACE inhibitors (ACEIs) have demonstrated consistent benefits in the treatment of HFrEF, reducing morbidity, mortality, and hospitalizations while improving quality of life. Robust evidence supports their use in both symptomatic and asymptomatic patients across a broad range of underlying etiologies. In the CONSENSUS trial, enalapril significantly reduced mortality among patients with severe HF (NYHA class IV).¹¹⁷ The SOLVD-Treatment and SOLVD-Prevention trials confirmed that enalapril reduced mortality and hospitalizations in symptomatic patients and delayed the onset of HF symptoms in individuals with asymptomatic LV dysfunction.^{118,119} Likewise, the SAVE trial showed that captopril reduced mortality and prevented progression to HF in patients with LV dysfunction following myocardial infarction.¹²⁰ The AIRE trial, with its findings confirmed during the AIRE Extension (AIREX) follow-up study, demonstrated that ramipril reduced mortality in patients with clinical signs of HF after myocardial infarction, with sustained long-term benefit.¹²¹ Together, these landmark studies established ACEIs as first-line therapy for HFrEF.

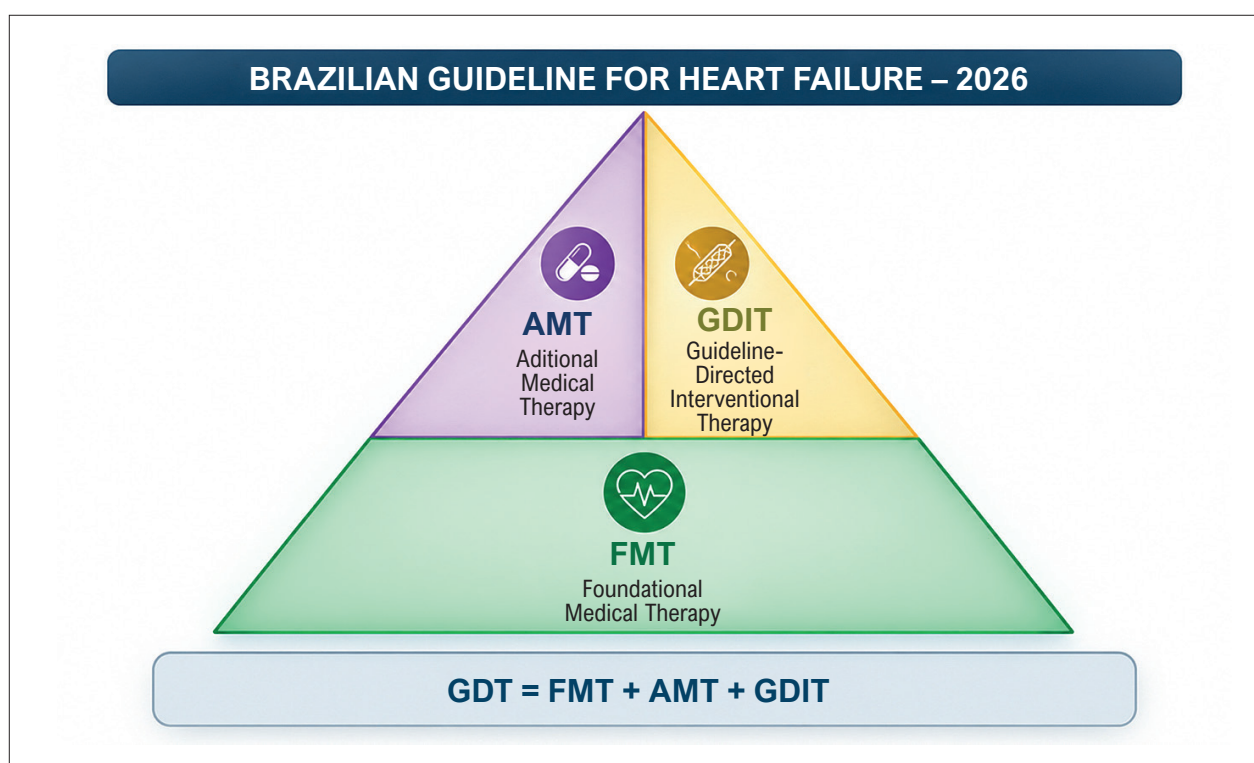


Figure 6.1 – Framework of Guideline-Directed Therapy (GDT) for the management of heart failure with reduced ejection fraction (HFrEF).

In patients intolerant to ACEIs because of persistent cough or angioedema, angiotensin II receptor blockers (ARBs) remain an effective and safe alternative, as demonstrated in the ELITE II and CHARM-Alternative trials.^{122,123} However, whenever feasible, replacement with an angiotensin receptor–neprilysin inhibitor (ARNI) should be preferred because of its superior efficacy in reducing mortality and HF hospitalizations.

Table 6.1 summarizes the recommendations for the use of ACEIs in patients with HFrEF.

6.1.3.2. Practical Considerations

ACEI intolerance is defined as the occurrence of persistent troublesome cough (approximately 10%–20% of patients) or angioedema (uncommon; < 1%). The rate of other adverse effects, including hypotension, hyperkalemia, and renal dysfunction, is similar for ACEIs and ARBs. In patients with persistent or recurrent hyperkalemia and/or progressive renal dysfunction associated with ACEIs, an alternative vasodilator therapy (typically the combination of hydralazine and a nitrate) should be considered.¹¹⁷

Table 6.1 – Recommendations for the use of angiotensin–converting enzyme inhibitors

Recommendation	Strength of recommendation	Certainty of evidence
In patients with asymptomatic left ventricular systolic dysfunction, we recommend IN FAVOR OF the use of an ACEI to reduce progression to symptomatic HF.	STRONG	HIGH
In patients with symptomatic HFrEF, we recommend IN FAVOR OF treatment with an ACEI, ARB, or ARNI (in patients intolerant to ACEIs) to improve symptoms and reduce hospitalizations and mortality.	STRONG	HIGH
In patients hospitalized for DHF, we recommend IN FAVOR OF the use of an ACEI to reduce all-cause mortality and HF rehospitalization.	STRONG	MODERATE

HF: heart failure; HFrEF: heart failure with reduced ejection fraction; ACEI: angiotensin–converting enzyme inhibitor; ARB: angiotensin II receptor blocker; ARNI: angiotensin receptor–neprilysin inhibitor.

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Given the risk of worsening renal function (WRF), hyperkalemia, and hypotension, ACEIs should be initiated at low doses (particularly in patients with borderline BP values) and gradually titrated to the target doses shown to provide clinical benefit in large multicenter trials.

An increase of up to 30% in baseline creatinine, an absolute creatinine concentration of up to 3.0 mg/dL, or an estimated creatinine clearance > 25 mL/min/m² is considered acceptable and does not require dose reduction of an ACEI or ARB. In these cases, close monitoring of renal function and serum potassium is recommended. If serum potassium exceeds 5.5 mEq/L, serum creatinine increases by $> 100\%$ or exceeds 3.5 mg/dL, or estimated creatinine clearance falls below 20 mL/min/m², discontinuation of the ACEI should be considered.¹²⁴

6.1.3.2. Beta-blockers

Beta-blockers consistently reduce mortality and hospitalizations in patients with HFrEF and improve symptoms in those with NYHA class II–IV. Robust evidence supports the use of bisoprolol, metoprolol succinate controlled release/extended release (CR/XL), and carvedilol.

In the CIBIS-II trial, bisoprolol reduced all-cause mortality (hazard ratio [HR], 0.66; 95% CI, 0.54–0.81) and was associated with a 45% reduction in SCD compared with placebo; the trial was terminated early because of the significant survival benefit.¹²⁵ In the MERIT-HF trial, metoprolol CR/XL reduced all-cause mortality (relative risk [RR], 0.66), decreased SCD by 41%, reduced cardiovascular mortality by 38%, and lowered the rate of HF hospitalizations.¹²⁶ In the COPERNICUS trial, carvedilol reduced the risk of death by approximately 35% in patients with severe HF and decreased the composite outcomes of death or cardiovascular hospitalization (27%) and death or HF hospitalization (31%).¹²⁷ In the head-to-head COMET trial, carvedilol was associated with lower mortality than metoprolol tartrate (34% vs. 40%; HR, 0.83; 95% CI, 0.74–0.93). However, these findings should not be extrapolated to metoprolol succinate, given the differences in formulation and dosing between the 2 preparations.¹²⁸ In older patients (aged ≥ 70 years) with a broad range of LVEFs, the SENIORS trial demonstrated that nebivolol reduced the primary composite endpoint of all-cause mortality or cardiovascular hospitalization (HR, 0.86; 95% CI, 0.74–0.99), with no reduction in all-cause mortality alone.¹²⁹

The clinical benefits of beta-blockers are not immediate. Reverse remodeling, with improvements in LVEF and symptoms, generally occurs only after weeks or months of treatment. Therefore, therapy should be initiated at low doses and gradually up-titrated while monitoring for bradycardia and signs of worsening congestion. If symptoms worsen during up-titration, diuretics and vasodilator therapy should be optimized before considering down-titration or discontinuation. In a meta-analysis including more than 10,000 patients, beta-blocker therapy prevented 3.8 deaths and 4 hospitalizations per 100 treated patients during the first year of treatment.¹³⁰

Corroborating these real-world findings, the PINNACLE registry (75,674 patients aged ≥ 65 years) confirmed a reduced risk of hospitalization or death (HR 0.83; 95% CI 0.80–0.86) and HF hospitalization (HR 0.78; 95% CI 0.74–0.83) with beta-blocker (BB) therapy.^{131,132}

Specifically within the LVEF range of 41–49%, this benefit appears to depend on baseline heart rhythm. Cleland et al.¹³³ observed a reduction in cardiovascular mortality with BB therapy among patients in sinus rhythm (HR 0.48; 95% CI 0.24–0.97; $p = 0.040$), but not among those with atrial fibrillation (HR 0.86; 95% CI 0.36–2.03; $p = 0.73$).¹³⁴

In all pharmacologic treatment strategies evaluated for HFrEF, the inclusion of a beta-blocker has consistently been associated with the greatest reductions in all-cause mortality, cardiovascular mortality (including SCD), and HF hospitalizations, confirming its central role in treatment.¹³⁵

Table 6.2 summarizes the recommendations for the use of beta-blockers in patients with HFrEF.

Practical considerations:

- Patients in more advanced NYHA functional classes should be re-evaluated with more frequent visits during initiation of beta-blocker therapy because of the risk of symptom worsening.
- Patients with pulmonary disease, including those with asthma (not experiencing an acute exacerbation), may receive beta-blocker therapy, preferably with β_1 -selective agents, such as bisoprolol or metoprolol succinate (depending on the dose).
- In patients with atrioventricular (AV) block or marked symptomatic bradycardia, the first step is to reduce or

Table 6.2 – Recommendations for the use of beta-blockers

Recommendation	Strength of recommendation	Certainty of evidence
In patients with symptomatic HFrEF, we recommend IN FAVOR OF treatment with bisoprolol, carvedilol, or metoprolol succinate to reduce morbidity and mortality.	STRONG	HIGH
In patients with asymptomatic left ventricular dysfunction following myocardial infarction, we recommend IN FAVOR OF treatment with a beta-blocker to reduce mortality and prevent the development of HF.	STRONG	HIGH

HF: heart failure; HFrEF: heart failure with reduced ejection fraction.

discontinue other AV nodal blocking medications, such as digoxin and amiodarone.

- Abrupt withdrawal of beta-blockers may lead to clinical deterioration and should be avoided unless clearly indicated, such as in the presence of cardiogenic shock (CS) and persistent symptomatic hypotension or bradycardia. In patients with asymptomatic hypotension, dose adjustment is unnecessary. If hypotension is accompanied by dizziness, vertigo, or confusion, the need for nitrates and other vasodilators should be reassessed, and these agents should be reduced or discontinued whenever possible. If symptoms persist, separating the administration times of HF medications or referral to a specialist should be considered.

6.1.3.3. Steroidal Mineralocorticoid Receptor Antagonists

Inhibition of aldosterone provides benefits beyond RAAS blockade, contributing to improvement in functional class, prevention of adverse cardiac remodeling, and reduction in the risk of SCD.

RCTs evaluating steroidal mineralocorticoid receptor antagonists (MRAs) – spironolactone and eplerenone – have demonstrated robust efficacy in patients with HFrEF across a broad range of etiologies and disease severity. The RALES trial (1999) was the first landmark study to demonstrate the benefits of spironolactone in patients with NYHA class III–IV, showing reductions of 30% in all-cause mortality, 36% in SCD, and 35% in HF hospitalizations.¹³⁶ Subsequently, the EMPHASIS-HF trial (2011) extended the indication to patients with milder symptoms (NYHA class II), demonstrating reductions of 24% in all-cause mortality and 37% in the composite endpoint of cardiovascular death or HF hospitalization.¹³⁷

In a post hoc analysis of TOPCAT, the subgroup of 520 patients with an LVEF of 44–49% showed a trend toward a reduction in the composite outcome of cardiovascular death, HF hospitalization, or aborted cardiac arrest with spironolactone (HR 0.72; 95% CI 0.50–1.05), particularly among patients enrolled in the Americas.¹³⁸

Treatment with a steroidal MRA is recommended for symptomatic patients with HFrEF (NYHA class II–IV), provided that those with an estimated glomerular filtration rate (eGFR) ≤ 30 mL/min/1.73 m² or serum potassium

≥ 5.5 mEq/L are excluded. Particular caution should be exercised when MRAs are used concomitantly with other medications that increase serum potassium levels or in clinical settings associated with dehydration.

The 2 steroidal MRAs differ in their pharmacologic profiles. Because spironolactone is less selective, it may cause painful gynecomastia and erectile dysfunction in men, as well as vaginal bleeding in women. Eplerenone, which is more selective, is associated with a lower rate of hormonal adverse effects. However, both agents carry a similar risk of hyperkalemia. The usual starting dose is 25 mg/day, with titration to 50 mg/day as tolerated. Patients with an eGFR of 31–49 mL/min/1.73 m² may receive a reduced starting dose of 12.5 mg/day. Renal function and serum potassium should be monitored frequently during the first weeks after treatment initiation and throughout follow-up.

Unlike the findings observed with steroidal mineralocorticoid receptor antagonists (sMRAs), the available evidence for nonsteroidal mineralocorticoid receptor antagonists (nsMRAs) in patients with LVEF $\leq 49\%$ derives from FINEARTS-HF, a trial conducted in a population with LVEF $\geq 40\%$ and a background therapy profile distinct from that of conventional HFrEF. Although the results suggest a consistent benefit of finerenone also at the lower end of this spectrum (LVEF $< 50\%$: rate ratio 0.84; 95% CI 0.68–1.03),¹³⁹ extrapolation of this finding to the HFrEF population should still be undertaken with caution. Specific studies are needed to confirm this benefit in patients already optimized on contemporary foundational therapies and to provide greater clarity regarding the role of finerenone across the phenotypic spectrum of the disease.

To date, no trials have demonstrated a benefit of nonsteroidal MRAs, such as finerenone, in patients with HFrEF.

Table 6.3 summarizes the recommendations for the use of steroidal MRAs in patients with HFrEF.

Practical considerations:

- The recommended starting dose of spironolactone, the standard agent in this class for HFrEF, is 25 mg once daily. The dose may be increased to 50 mg once daily if symptoms persist and renal function and serum potassium levels allow dose escalation.
- Renal function and serum potassium levels should be closely monitored. If serum potassium increases, the dose may be reduced to 12.5 mg once daily or

Table 6.3 – Recommendations for the use of mineralocorticoid receptor antagonists in patients with heart failure with reduced ejection fraction

Recommendation	Strength of recommendation	Certainty of evidence
In patients with symptomatic HFrEF, we recommend IN FAVOR OF treatment with spironolactone or eplerenone to reduce mortality and morbidity.	STRONG	HIGH
In patients with an eGFR ≤ 30 mL/min/1.73 m ² or serum potassium ≥ 5.5 mEq/L, we recommend AGAINST the initiation of spironolactone or eplerenone.	STRONG	HIGH

HFrEF: heart failure with reduced ejection fraction; eGFR: estimated glomerular filtration rate.

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even 12.5 mg every other day, which was the lowest recommended dose used in the RALES trial.

- In patients experiencing steroid-related adverse effects, such as painful gynecomastia that precludes continued use of spironolactone, eplerenone may be substituted at equivalent doses.

6.1.3.4. Angiotensin Receptor-Neprilysin Inhibitor

Sacubitril-valsartan, an ARNI, combines an ARB (valsartan) with a neprilysin inhibitor (sacubitril). This therapy promotes vasodilation, natriuresis, and diuresis, increases GFR and renal blood flow, suppresses renin and aldosterone release, reduces sympathetic activity, and exerts antihypertrophic and antifibrotic effects, all of which contribute to its therapeutic benefits in HFrEF.

The PARADIGM-HF trial evaluated outpatients with chronic symptomatic HFrEF (LVEF $\leq$ 40%, elevated NT-proBNP levels, and clearance $\geq$ 30 mL/min/1.73 m²) receiving optimal therapy including ACEIs. In this population, sacubitril-valsartan at maximum doses was superior to enalapril in reducing cardiovascular mortality (HR, 0.80; 95% CI, 0.71–0.89), HF hospitalizations (HR, 0.79; 95% CI, 0.71–0.89), and all-cause mortality (HR, 0.84; 95% CI, 0.76–0.93). It also reduced SCD and demonstrated a more favorable renal safety profile.¹⁴⁰ Based on these findings, replacement of an ACEI with an ARNI started to be recommended for patients with HFrEF who remain symptomatic despite receiving the maximum tolerated doses of a beta-blocker, MRA, and ACEI or ARB. However, limitations of the PARADIGM-HF trial should be acknowledged. The run-in phase before randomization excluded patients intolerant to the medications; the dose of enalapril used was below the maximum recommended dose in some participating centers; and the study included relatively few Black patients, as well as limited numbers of patients with advanced HF (NYHA class IV) or recent clinical instability. These factors limit the generalizability of the findings to patients with more advanced disease or lower treatment tolerance. Therefore, although the recommendation is strong, the certainty of evidence should be considered moderate.

A pooled analysis of the PARAGON-HF and PARADIGM-HF trials suggested that sacubitril/valsartan is associated with a reduction in the composite outcome of HF hospitalization or cardiovascular death among patients with an LVEF of 41–49%, with a more pronounced effect in women.¹⁴¹ Corroborating this finding, a meta-analysis combining the PARAMOUNT-HF and PARAGON-HF trials demonstrated, specifically in this population with an LVEF of 41–49%, a reduced risk of the same composite outcome with sacubitril/valsartan compared with valsartan alone (HR 0.65; 95% CI 0.45–0.92).¹⁴²

In patients hospitalized for DHE, early initiation of an ARNI after clinical stabilization has been shown to be safe in studies specifically designed for this clinical setting. The multicenter PIONEER-HF trial, conducted in the United States with an 8-week follow-up, demonstrated that initiation of sacubitril-valsartan during hospitalization in patients admitted as profile B resulted in a greater reduction in the

primary outcome (NT-proBNP) at 8 weeks, with no increase or decrease in adverse events compared with enalapril.¹⁴³

The prospective, multicenter, open-label TRANSITION study evaluated clinically stabilized patients after a recent episode of DHE (BP $\geq$ 110 mm Hg), comparing initiation of sacubitril-valsartan before versus after hospital discharge. Most patients achieved the target dose within 10 weeks, with an acceptable safety profile and no differences between the groups.¹⁴⁴ This evidence suggests the possibility of early initiation of ARNI therapy during hospitalization.

In addition to clinical outcomes, there is evidence of a favorable impact on biomarkers and LV reverse remodeling. The prospective, multicenter, single-arm (sacubitril-valsartan) PROVE-HF study, conducted in the United States, demonstrated an early and sustained reduction in NT-proBNP concentrations (approximately 37% at 14 days), accompanied by improvements in NYHA functional class and Kansas City Cardiomyopathy Questionnaire (KCCQ) scores, which showed a weak but significant correlation with improvements in markers of cardiac volume and function at 12 months.¹⁴⁵

Subsequent studies, including LIFE and PARADISE-MI, did not demonstrate unequivocal benefit of ARNI therapy in settings of advanced HF or post-myocardial infarction, suggesting that the benefit may be limited in patients with more severe or clinically unstable disease.

Table 6.4 summarizes the recommendations for the use of sacubitril-valsartan in patients with HFrEF.

Practical Considerations:

- When initiating sacubitril-valsartan, a 36-hour washout period is mandatory after the last dose of an ACEI because of the risk of angioedema. This precaution is not required when switching from an ARB. Sacubitril-valsartan is contraindicated in patients with a history of angioedema (related to ACEI/ARB or hereditary/idiopathic). Treatment should be initiated only in stable patients with a systolic BP (SBP) $\geq$ 100 mm Hg, an eGFR $\geq$ 30 mL/min/1.73 m², and serum potassium $<$ 5.2 mEq/L. Depending on the clinical context, the recommended starting dose is 50 mg or 100 mg twice daily, with gradual titration as tolerated to the target dose of 200 mg twice daily. Careful monitoring of BP, renal function, and serum potassium is essential at treatment initiation, after each dose escalation, and periodically during follow-up. In euvolemic patients, adjustment of diuretic therapy should be considered to prevent hypotension (Table 6.4).

6.1.3.5. Sodium-Glucose Cotransporter 2 Inhibitors

Evidence showing reductions in hospitalizations and all-cause mortality supports the use of SGLT2 inhibitors in the treatment of HF, establishing this drug class as one of the most effective therapies for reducing adverse events in HF.

The DAPA-HF trial randomly assigned 4744 patients with HF, LVEF $\leq$ 40%, and elevated NP levels or prior hospitalization to receive dapagliflozin or placebo. The composite outcome of worsening HF or cardiovascular death

Table 6.4 – Recommendations for the use of sacubitril-valsartan in patients with heart failure with reduced ejection fraction

Recommendation	Strength of recommendation	Certainty of evidence
In outpatients with symptomatic HFrEF, despite optimal guideline-directed medical therapy, we recommend IN FAVOR OF the replacement of an ACEI or ARB with an ARNI to reduce cardiovascular mortality, HF hospitalizations, and symptoms.	STRONG	MODERATE
In patients hospitalized for worsening chronic HFrEF despite prior optimal medical therapy, we recommend IN FAVOR OF the replacement of an ACEI or ARB with an ARNI after hemodynamic stabilization (SBP > 100 mm Hg) and before hospital discharge to reduce rehospitalizations, improve biomarkers, and facilitate early achievement of the target dose.	STRONG	MODERATE
In patients with newly diagnosed symptomatic HFrEF without previous use of ACEIs, we recommend IN FAVOR OF the initiation of RAAS blockade with an ARNI to provide earlier and potentially greater clinical benefits and to reduce morbidity and mortality.	WEAK	LOW

HF: heart failure; HFrEF: heart failure with reduced ejection fraction; SBP: systolic blood pressure; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; ARNI: angiotensin receptor-neprilysin inhibitor; RAAS: renin-angiotensin-aldosterone system.

occurred in 16.3% of patients in the dapagliflozin group and 21.2% in the placebo group (HR, 0.74; 95% CI, 0.65–0.85; $p < 0.001$).¹⁴⁶ However, the analysis of the effect on all-cause mortality yielded borderline results.

In the EMPEROR-Reduced trial, which enrolled 3730 patients with LVEF $\leq 40\%$ and elevated NP levels or prior hospitalization, the composite endpoint of cardiovascular death or HF hospitalization occurred in 19.4% of patients receiving empagliflozin and 24.7% of those receiving placebo (HR, 0.75; 95% CI, 0.65–0.86; $p < 0.001$).¹⁴⁷ In both cases, the benefit was consistent regardless of the presence of type 2 diabetes. Under optimal medical therapy, there was no reduction in all-cause mortality, and the benefit observed for the composite endpoint was driven by a reduction in hospitalizations.

The EMPULSE trial evaluated initiation of empagliflozin during hospitalization for DHF after clinical stabilization in a relatively small cohort ($n = 530$) that included patients with LVEF $\leq 40\%$ and $> 40\%$. Initiation of therapy approximately 3 days after hospital admission resulted in a significant improvement in the hierarchical composite clinical outcome at 90 days (win ratio, 1.36; 95% CI, 1.09–1.68; $p = 0.0054$), including reductions in all-cause mortality and HF events, as well as improvements in quality of life, without an increase in serious adverse events.¹⁴⁸ These findings support the feasibility and safety of early in-hospital initiation of SGLT2 inhibitors.

A meta-analysis combining the DAPA-HF and EMPEROR-Reduced trials ($n = 8474$) showed reductions of 13% in all-cause mortality (HR, 0.87; 95% CI, 0.77–0.98), 14% in cardiovascular mortality (HR, 0.86; 95% CI, 0.76–0.98), 26% in cardiovascular death or first HF hospitalization (HR, 0.74; 95% CI, 0.68–0.82), and 25% in the composite of recurrent HF hospitalizations or cardiovascular death (HR, 0.75; 95% CI, 0.68–0.84).²⁹ The event curves separate in the first few weeks, reinforcing the early benefit. However,

there are differences between the populations included in the 2 studies. In addition to their clinical efficacy, SGLT2 inhibitors provide important renal benefits in HFrEF, with a slower annual decline in GFR, decrease in hyperkalemia, and reduction in major adverse renal outcomes, irrespective of type 2 diabetes status.¹⁴⁹

For the LVEF range of 41–49%, evidence on SGLT2 inhibitors is derived from the same trials designed for HFpEF (EMPEROR-Preserved, DELIVER, and SOLOIST-WHF), in which this population was included as a prespecified subgroup.^{150–152} A meta-analysis pooling all cardiovascular outcome trials of SGLT2 inhibitors demonstrated, in this subgroup, a 20% reduction in the composite outcome of cardiovascular death or worsening HF ($p < 0.001$), driven by a 26% reduction in worsening HF events, again without a significant reduction in cardiovascular mortality. This pattern differs from that observed in classic HFrEF (LVEF $\leq 40\%$), for which the DAPA-HF/EMPEROR-Reduced meta-analysis has demonstrated reductions in both all-cause and cardiovascular mortality.¹⁵³

In the SOLOIST-WHF trial,¹⁵⁴ patients with type 2 diabetes hospitalized for worsening HF experienced a significant reduction in the primary composite outcome of cardiovascular death, HF hospitalizations, and urgent HF visits when treated with sotagliflozin compared with placebo (HR, 0.67; 95% CI, 0.52–0.85; $p < 0.001$). Furthermore, a post hoc follow-up analysis demonstrated reductions in these outcomes through 30 and 90 days after hospital discharge.¹⁵⁰ The SCORED trial, conducted in patients with type 2 diabetes, chronic kidney disease (CKD), and additional cardiovascular risk, showed that sotagliflozin significantly reduced the primary composite endpoint of cardiovascular death, HF hospitalizations, and urgent HF visits compared with placebo (HR, 0.74; 95% CI, 0.63–0.88; $p < 0.001$).¹⁵⁵ At the time of publication of this guideline, sotagliflozin was not available for use in Brazil.

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Table 6.5 summarizes the recommendations for the use of SGLT2 inhibitors in patients with HFrEF.

Practical Considerations:

- The usual dose of dapagliflozin is 10 mg once daily, and the recommended dose of empagliflozin is likewise 10 mg once daily, without the need for specific titration for HF. These medications may be initiated even in patients with impaired renal function, provided the eGFR is ≥ 20 mL/min/1.73 m². A transient decline in eGFR commonly occurs shortly after treatment initiation, which is generally mild and self-limited. In the long term, however, SGLT2 inhibitors slow the decline in renal function and reduce the risk of major adverse renal outcomes.¹⁵⁶ Therapy may be continued even if eGFR subsequently falls below the initiation threshold, provided no clinically significant adverse effects occur. The most common adverse events associated with this drug class are genitourinary infections, particularly genital candidiasis and mild urinary tract infections. Patients should be counseled regarding appropriate genital hygiene, early recognition of symptoms, and the importance of seeking prompt medical attention if infection develops. SGLT2 inhibitors may be initiated together with the other core pillars of GDMT for HFrEF, including early after clinical stabilization (Table 6.5).

6.1.4. Additional Medical Therapy for HFrEF

6.1.4.1. Diuretics

The use of diuretics in HFrEF predates the era of evidence-based medicine, and their effects on morbidity and mortality have not been conclusively established. Consequently, they should not be used as outpatient monotherapy. Relief of systemic and pulmonary congestion results in substantial

clinical improvement. Congestion also contributes to the development of renal and hepatic dysfunction. Therefore, effective decongestion improves quality of life and mitigates cardiorenal syndrome (CRS).

Although robust evidence demonstrating a prognostic benefit of diuretics in HF is lacking, their use is supported by a strong pathophysiological rationale, consistent clinical experience, and their inclusion in virtually all landmark RCTs evaluating contemporary therapies for HFrEF. Diuretic therapy should be individualized according to the severity of congestion and the patient's clinical response. The lowest effective dose to maintain euvolemia is recommended.

The ReBic-1 trial, conducted in Brazil, randomly assigned clinically stable patients with chronic HFrEF receiving diuretics to either diuretic maintenance or withdrawal. After 90 days, there were no significant differences in rates of diuretic reuse, mortality, or hospitalization, suggesting that withdrawal of diuretics may be safe and should be considered in stable patients with no signs of congestion.¹⁵⁷

Loop diuretics are preferred over thiazide diuretics because of their greater potency and efficacy in decongestion. It should also be recognized that drugs used in the treatment of HFrEF, such as ACEIs, ARBs, MRAs, ARNIs, and SGLT2 inhibitors, exert modest diuretic effects. Patients with loop diuretic resistance may benefit from the synergistic combination of a loop diuretic with a thiazide diuretic.

In the outpatient setting, patients who remain congested despite adequate doses of a loop diuretic may benefit from the addition of a diuretic from another class, such as a thiazide diuretic (eg, hydrochlorothiazide or chlorthalidone), to achieve sequential nephron blockade and enhance natriuresis. Clinical trials in the outpatient setting, such as the DEA-HF trial, demonstrated greater diuresis and natriuresis with combined loop and thiazide therapy but also reported an increased risk of renal dysfunction. Therefore, combination diuretic therapy should be reserved for refractory congestion and accompanied by close laboratory

Table 6.5 – Recommendations for the use of sodium–glucose cotransporter 2 inhibitors in patients with heart failure with reduced ejection fraction

Recommendation	Strength of recommendation	Certainty of evidence
In patients with symptomatic HFrEF, regardless of the presence of diabetes, we recommend IN FAVOR OF treatment with an SGLT2 inhibitor (dapagliflozin or empagliflozin) to reduce the risk of the composite outcome of HF hospitalization or cardiovascular death.	STRONG	HIGH
In patients with newly diagnosed symptomatic HFrEF with no prior GDMT, we recommend IN FAVOR OF the initiation of an SGLT2 inhibitor (dapagliflozin or empagliflozin) to provide earlier and potentially greater clinical benefits and to reduce the substantial morbidity and mortality associated with the disease.	WEAK	LOW
In patients with HFrEF who are already receiving GDMT and hospitalized for worsening HF, we recommend IN FAVOR OF the initiation of an SGLT2 inhibitor (dapagliflozin or empagliflozin) after clinical stabilization to improve clinical outcomes and relieve symptoms.	STRONG	MODERATE

HF: heart failure; HFrEF: heart failure with reduced ejection fraction; GDMT: guideline-directed medical therapy; SGLT2: sodium–glucose cotransporter 2.

monitoring, particularly of renal function and serum electrolytes, because of the increased risks of hypokalemia, hyponatremia, and acute kidney injury.¹⁵⁸

A recent meta-analysis evaluating thiazide diuretics as adjunctive therapy to loop diuretics in patients with refractory HF also demonstrated significantly improved decongestion, albeit at the expense of a higher risk of fluid and electrolyte disturbances and renal function deterioration, reinforcing the need for careful patient selection and close monitoring.¹⁵⁹

Table 6.6 summarizes the recommendations for the use of diuretics in patients with HFrEF.

6.1.4.2. Angiotensin II Type 1 Receptor Blockers

ARBs are indicated primarily for patients who are intolerant to ACEIs because of persistent cough or angioedema, or for those who do not have access to sacubitril-valsartan.

The ELITE II trial (2000) compared losartan with captopril in 3152 patients with HF (NYHA class II–IV) and LVEF $\leq$ 40%. Losartan did not demonstrate superiority over captopril: all-cause mortality was similar between groups (11.7% vs. 10.4%; HR, 1.13; 95% CI, 0.95–1.35; $p = 0.16$). Although losartan was better tolerated, it did not reduce all-cause mortality compared with ACEI therapy.¹²² It should be noted that the trial was not designed to test non-inferiority.

In the Val-HeFT trial, 5010 patients with NYHA class II–IV HF were randomly assigned to receive valsartan 160 mg twice daily or placebo. Although all-cause mortality was similar in the 2 groups, the composite outcome of mortality and morbidity was reduced with valsartan (HR, 0.87; 95% CI, 0.79–0.96; $p = 0.009$), largely due to a reduction in HF hospitalizations.¹⁶⁰ In a post hoc analysis, the benefit was more consistent in patients not receiving ACEIs, whereas the combination of ACEI + ARB + beta-blocker provided no additional benefit and raised safety concerns.

The CHARM-Alternative trial evaluated candesartan (up to 32 mg) in 2028 patients intolerant to ACEIs (LVEF $\leq$ 40%). Candesartan significantly reduced the primary composite outcome of cardiovascular death or HF hospitalization (33% vs. 40%; RR, 0.70; 95% CI, 0.60–0.81; $p < 0.0001$) compared with placebo. However, there was no unequivocal reduction in all-cause mortality, reinforcing

the role of ARBs as an alternative for patients who cannot tolerate ACEIs.¹²³

In a subgroup analysis of the CHARM program, the 1,322 patients with an LVEF of 41–49% experienced a reduction in HF hospitalizations of a magnitude similar to that observed in classic HFrEF (incidence rate ratio, 0.48 [95% CI, 0.33–0.70; $p < 0.001$] vs. 0.68 [95% CI, 0.58–0.80; $p < 0.001$], respectively).¹⁶¹

The HEAAL study compared losartan 150 mg vs. 50 mg in 3846 patients intolerant to ACEIs. The 150 mg dose reduced the composite outcome of all-cause mortality or HF hospitalization (43% vs. 46%; HR, 0.90; 95% CI, 0.82–0.99; $p = 0.027$), an effect driven primarily by the reduction in HF hospitalizations, with no isolated impact on all-cause mortality.¹⁶²

Overall, ARBs have not demonstrated superiority over ACEIs, nor have they consistently reduced all-cause mortality. Nevertheless, large RCTs have shown them to be non-inferior, with their principal clinical benefit being a reduction in HF hospitalizations, particularly among patients who are intolerant to ACEIs or who do not have access to sacubitril-valsartan. It should also be recognized that sacubitril-valsartan provides an option to replace an ACEI in cases of intolerance due to cough. Therefore, ARBs should be considered a safe and effective treatment option in these specific clinical settings. Concomitant use of an ACEI and an ARB should be avoided because of the higher incidence of adverse effects without additional benefit.

Table 6.7 summarizes the recommendations for the use of ARBs in patients with HFrEF.

6.1.4.3. If Channel Inhibitor

Ivabradine selectively inhibits the *If* channels in the sinoatrial node, reducing HR without directly affecting contractility or BP. Its clinical benefit depends on the presence of sinus rhythm, thus being ineffective in AF or atrial flutter.

In the SHIFT trial, ivabradine was added to standard medical therapy, including beta-blockers, in symptomatic patients (NYHA class II–IV) in sinus rhythm, with HR $\geq$ 70 beats per minute (bpm), and LVEF $\leq$ 35%, and was associated with a reduction in the composite endpoint of cardiovascular

Table 6.6 – Recommendations for the use of diuretics in patients with heart failure with reduced ejection fraction

Recommendation	Strength of recommendation	Certainty of evidence
In patients with symptomatic HFrEF and evidence of congestion, we recommend IN FAVOR OF treatment with a loop diuretic to reduce congestion and improve symptoms.	STRONG	LOW
In patients with HFrEF and persistent congestion despite optimal medical therapy, we recommend IN FAVOR OF the addition of a thiazide diuretic.	WEAK	LOW
In patients receiving diuretic therapy, we recommend IN FAVOR OF periodic reassessment of the diuretic indication and dose according to volume status.	STRONG	MODERATE

HFrEF: heart failure with reduced ejection fraction.

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Table 6.7 – Recommendations for the use of angiotensin II receptor blockers in patients with heart failure with reduced ejection fraction

Recommendation	Strength of recommendation	Certainty of evidence
In patients with HFrEF who are intolerant to ACEIs, we recommend IN FAVOR OF the replacement of the ACEI with an ARB to reduce the composite outcome of cardiovascular death or HF hospitalization.	STRONG	MODERATE

HF: heart failure; HFrEF: heart failure with reduced ejection fraction; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker.

death or HF hospitalization, with a consistent reduction in HF hospitalizations. There was no statistically significant reduction in all-cause mortality, but the benefit was more pronounced in patients with a baseline HR ≥ 75 bpm and in those not receiving target doses of beta-blockers.^{163,164}

Subsequent meta-analyses have confirmed these findings, consistently demonstrating that ivabradine reduces the risk of HF hospitalization.^{165,166}

Regarding safety, ivabradine was generally well tolerated in the SHIFT trial, with a relatively low incidence of adverse events. The most common adverse effects were bradycardia, observed in approximately 5% of patients, and a slight increase in AF. These findings warrant a careful re-evaluation of the indication for ivabradine in patients with paroxysmal AF.

Table 6.8 summarizes the recommendations for the use of ivabradine in patients with HFrEF

6.1.4.4. Combination Therapy with Hydralazine and Isosorbide Dinitrate

The rationale for the combined use of hydralazine and isosorbide dinitrate (H-ISDN) is the simultaneous reduction of preload (nitrate) and afterload (hydralazine). In addition, this combination may exert clinically relevant pleiotropic effects. Hydralazine inhibits peroxynitrite formation, reducing oxidative stress and preserving nitric oxide (NO)-dependent signaling.¹⁶⁷ This mechanism helps restore NO bioavailability, mitigate endothelial dysfunction, and attenuate nitrate tolerance, contributing to more sustained vasodilation and potentially to the favorable clinical outcomes observed in clinical trials.

The combination of H-ISDN has demonstrated a reduction in mortality in HFrEF since the 1980s. In the V-HeFT I trial, H-ISDN reduced mortality compared with placebo (2-year mortality, 25.6% vs. 34.3%; 3-year mortality, 36.2% vs. 46.9%; ~36% relative reduction at 3 years).¹⁶⁸ However, in the V-HeFT II trial, enalapril was superior to H-ISDN in reducing 2-year mortality (18% vs. 25%; $p = 0.016$), establishing the primacy of ACEIs over direct vasodilators.¹⁶⁸

In the A-HeFT trial, which enrolled self-identified Black patients with NYHA class III or IV HFrEF receiving optimal medical therapy, the addition of fixed-dose H-ISDN reduced all-cause mortality by 43% and HF hospitalizations by 33%, while also improving quality of life. The study was terminated early because of the clear clinical benefit.¹⁷⁰ Consistent improvements in outcomes have been observed particularly in self-identified Black patients with advanced symptomatic HFrEF (NYHA class III–IV) receiving optimal medical therapy, patients intolerant to ACEIs or ARBs, and patients with restr.

Practical Considerations:

In addition to its indication for individuals of African descent, the combination of H-ISDN may be a useful alternative when treatment with an ACEI, ARB, or ARNI is not feasible, such as in patients with persistent hyperkalemia or WRF, although it offers no mortality benefit.

Table 6.9 summarizes the recommendations for the use of H-ISDN in patients with HFrEF.

Digoxin is the cardiovascular agent with the longest continuous use in modern medicine. After decades of progressive decline, with prescriptions decreasing from

Table 6.8 – Recommendations for the use of ivabradine in patients with heart failure with reduced ejection fraction

Recommendation	Strength of recommendation	Certainty of evidence
In patients with symptomatic heart failure with reduced ejection fraction, left ventricular ejection fraction $< 35\%$, sinus rhythm, heart rate ≥ 70 bpm, and receiving optimal medical therapy including a beta-blocker at the maximum tolerated dose, we recommend IN FAVOR OF treatment with ivabradine to improve symptoms and reduce hospitalizations.	STRONG	MODERATE

Table 6.9 – Recommendations for the combined use of hydralazine and isosorbide dinitrate in patients with heart failure with reduced ejection fraction

Recommendation	Strength of recommendation	Certainty of evidence
In self-identified Black patients with HFrEF, NYHA class III or IV, and receiving optimal medical therapy, we recommend IN FAVOR OF the addition of hydralazine and isosorbide dinitrate to reduce mortality, symptoms, and hospitalizations.	STRONG	MODERATE
In patients with HFrEF who are intolerant to ACEIs, ARBs, or ARNIs, including renal dysfunction (creatinine > 2.5 mg/dL) or persistent hyperkalemia (potassium > 5.5 mEq/L), we recommend IN FAVOR OF treatment with hydralazine and isosorbide dinitrate as an alternative therapeutic strategy.	STRONG	MODERATE
In patients with HFrEF refractory to optimal medical therapy, regardless of ethnicity, hydralazine plus isosorbide dinitrate might be considered as an adjunctive treatment strategy.	WEAK	LOW

HFrEF: heart failure with reduced ejection fraction; NYHA: New York Heart Association; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; ARNI: angiotensin receptor-neprilysin inhibitor.

33.1% to 10.7% between 2005 and 2014,¹⁷² emerging evidence has prompted a reassessment of its therapeutic role. This decline was driven largely by the predominantly negative interpretation of the DIG trial,¹⁷³ due to concerns about toxicity at higher doses and the introduction of new therapies. However, it is important to recognize that the DIG trial, which enrolled more than 6800 symptomatic patients in sinus rhythm with LVEF ≤ 45%, demonstrated a significant reduction in both overall hospitalizations and hospitalizations for worsening HF, despite no reduction in all-cause mortality.

More recently, 2 RCTs of patients receiving contemporary optimal medical therapy have provided important new evidence. The DIGIT-HF trial enrolled 1212 patients with advanced HFrEF (predominantly NYHA class III–IV, mean LVEF 29%) and demonstrated that low-dose digitoxin significantly reduced the primary composite outcome of all-cause mortality or first hospitalization for worsening HF (HR, 0.82; 95% CI, 0.69–0.98; $p = 0.03$). The benefit was consistent across predefined subgroups, including patients receiving quadruple therapy.¹⁷⁴

The DECISION trial evaluated low-dose digoxin in 1001 patients with less severe HFrEF or HFmrEF (predominantly NYHA class II), with a high prevalence of ARNI (53%) and SGLT2 inhibitor (41%) use. Although the primary outcome did not reach statistical significance in the intention-to-treat analysis (RR, 0.81; 95% CI, 0.61–1.07; $p = 0.133$), the on-treatment analysis, which adjusted for the high discontinuation rate, demonstrated a significant reduction (RR, 0.66; 95% CI, 0.47–0.92; $p = 0.015$), consistent with the benefit signal observed in previous studies.¹⁷⁵

A meta-analysis by Damman et al., which pooled data from the 3 major RCTs (DIG, DIGIT-HF, and DECISION; $n = 9013$), demonstrated a significant reduction in the composite endpoint of cardiovascular death or first worsening HF event (HR, 0.85; 95% CI, 0.80–0.90;

$p < 0.001$). There was no significant heterogeneity among the studies or interaction with the extent of HF background therapy.¹⁷⁶ The reduction was driven primarily by a decrease in worsening HF events (HR, 0.75; 95% CI, 0.69–0.81; $p < 0.001$). No significant effect was observed on cardiovascular mortality alone (HR, 0.99) or all-cause mortality (HR, 0.97), a pattern similar to that reported with ivabradine, which has been incorporated into standard therapy based on comparable outcomes.

An important clinical finding emerged from the prespecified digoxin withdrawal analysis of the DECISION trial. Discontinuation of long-term low-dose digoxin was associated with a more than 7-fold increase in the rate of cardiovascular events during the subsequent 6 weeks (42.8 vs. 5.9 events per 100 patient-years; RR, 7.37; 95% CI, 1.56–34.88; $p = 0.012$). This increase was accompanied by an increase in HR, reduction in SBP, rise in NT-proBNP, and reduction in renal function, despite the fact that 86% of patients were receiving beta-blockers, 88% were receiving RAAS blockers, and 72% were receiving SGLT2 inhibitors.¹⁷⁷ These findings suggest that the hemodynamic and neurohormonal benefits of digoxin persist even in patients receiving contemporary optimal medical therapy and that routine withdrawal of digoxin cannot be considered a safe strategy.

Dosing and Safety: the benefits of digitalis glycosides appear to be limited to low serum concentrations. For digoxin, the recommended target dose ranges from 0.5 to 0.9 ng/mL, and values above 1.2 ng/mL should be avoided. Dose adjustment should consider renal function, age, and body weight, with periodic monitoring of serum levels. Digitoxin, evaluated in the DIGIT-HF trial, has a predominant hepatic clearance, thus enhancing stability in patients with renal dysfunction. However, digitoxin is not currently available in Brazil (Table 6.10).

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6.1.5. General Principles for the Initiation and Optimization of Medical Therapy for HFrEF

The pharmacologic treatment of HFrEF is based on robust evidence demonstrating that inhibition of the principal pathophysiological, neurohormonal, and inflammatory mechanisms modifies the natural history of the disease.

In patients with HFrEF, the primary treatment goals are to:

- Relieve symptoms and improve functional capacity;
- Reduce HF hospitalizations;
- Slow disease progression and improve survival.

Pharmacologic management is centered on the prioritized use of four drug classes with well-established benefits in reducing morbidity and mortality and modifying the course of the disease, collectively referred to in this guideline as foundational medical therapy (FMT), namely:

1. ACEIs, ARBs, or ARNIs (sacubitril-valsartan);
2. Beta-blockers;
3. MRAs (spironolactone or eplerenone);
4. SGLT2 inhibitors.

6.1.5.1. Dose Titration Strategy

The primary objective of up-titration is to achieve the target doses of therapies with proven clinical benefit as rapidly, safely, and individually as possible, *ideally within 8 weeks* of diagnosis or stabilization after an episode of decompensation. Dose titration should be tailored to each patient's clinical status and treatment tolerance, ideally accompanied by frequent follow-up visits, as illustrated in Figure 6.2. Even in stable patients, initiation and up-titration of therapy should follow a strategy that prioritizes medications according to their prognostic impact, avoiding polypharmacy and therapeutic duplication. Clinical and laboratory responses should be reassessed within 3–6

months, allowing treatment adjustments and escalation to other drugs—additional medical therapy (AMT)—or device implantation—guideline-directed interventional therapy (GDIT)—according to the therapeutic response (Figure 6.2). Chart 6.1 summarizes the initial and target doses of medications used in the treatment of HFrEF.

6.1.5.2. Titration Sequence

Given the number of drugs available for the contemporary management of HFrEF, numerous treatment combinations are theoretically possible (Figure 6.2). However, treatment selection should not be arbitrary. The guiding principle is that treatment should begin with the foundational disease-modifying therapies, either through a stepwise approach or, whenever feasible, a rapid parallel up-titration strategy, with early and concomitant initiation while accounting for each patient's phenotype and individual tolerance. Traditionally, ACEIs/ARBs, beta-blockers, and MRAs were introduced sequentially, reflecting the chronology reported in the landmark clinical trials. In contrast, ARNIs and SGLT2 inhibitors were evaluated in patients who remained symptomatic, had elevated NT-proBNP, or had been recently hospitalized despite already receiving the other drug classes.

To date, no clinical trials have directly evaluated the simultaneous initiation of a beta-blocker, an RAAS inhibitor (ACEI, ARB, or ARNI), an MRA, and an SGLT2 inhibitor. The rationale for this strategy is currently based on extrapolations and indirect comparisons, including the PROVE-HF study (ARNI),¹⁴⁵ the STRONG-HF trial (beta-blocker + RAAS inhibitor + MRA, with approximately 10% of patients also receiving an SGLT2 inhibitor), and findings from network meta-analyses.

Nevertheless, early integration of these therapies is supported by observational data and by the early separation

Table 6.10 – Recommendations for the use of digoxin in patients with heart failure with reduced ejection fraction

Recommendation	Strength of recommendation	Certainty of evidence
In patients with symptomatic HFrEF (NYHA class II–IV) in sinus rhythm or atrial fibrillation, receiving optimal medical therapy, we recommend IN FAVOR OF treatment with low-dose digoxin to reduce hospitalizations for worsening HF and the composite outcome of cardiovascular death or worsening HF.	STRONG	MODERATE
We recommend IN FAVOR OF a target serum digoxin concentration of 0.5–0.9 ng/mL, with individualized dose adjustment according to renal function, age, and body weight, to maximize clinical benefit while minimizing toxicity.	STRONG	MODERATE
In patients with stable HFrEF receiving long-term digoxin therapy, we recommend AGAINST routine withdrawal of digoxin because of the documented risk of acute clinical deterioration, even in patients receiving optimal quadruple therapy.	STRONG	MODERATE
In patients with HFrEF and atrial fibrillation who have inadequate ventricular response despite optimal beta-blocker therapy, or in whom beta-blockers are contraindicated, we recommend IN FAVOR OF treatment with digoxin for ventricular response control.	STRONG	MODERATE

HF: heart failure; HFrEF: heart failure with reduced ejection fraction; NYHA: New York Heart Association.

of event curves observed in the landmark trials evaluating each therapeutic class individually.

In patients who remain symptomatic (NYHA class II–IV) after 3 to 6 months of appropriate optimization, additional therapies (ivabradine, digoxin, or H-ISDN) should be considered, as should referral to a specialized advanced HF center, in accordance with the therapeutic algorithm shown in Figure 6.2.

6.1.5.3. Hospitalization as an Opportunity for Treatment Optimization

Hospitalization for decompensated chronic HF as well as the early vulnerable post-discharge period represent a critical opportunity to initiate or optimize medical therapy.

The STRONG-HF trial demonstrated reductions in mortality and HF rehospitalization when optimization with an ACEI/ARB (or ARNI), beta-blocker, and MRA was initiated during hospitalization, with a goal of complete up-titration within 6 weeks. The PIONEER-HF and TRANSITION studies confirmed the safety of early in-hospital initiation of ARNI

therapy, demonstrating rapid reduction in NT-proBNP without an increase in adverse events.^{143,144}

6.1.5.4. Initiation of Foundational Medical Therapy in Treatment-Naïve Patients

For patients with newly diagnosed symptomatic HFrEF, initiation of therapy with an ACEI, beta-blocker, and MRA is strongly recommended and supported by high-certainty evidence. In this same clinical setting, initiation of an ARNI, as a replacement for an ACEI, and an SGLT2 inhibitor is weakly recommended and supported by low-certainty evidence, since no prospective, randomized, double-blind controlled trials have specifically evaluated these agents as initial therapy for HFrEF (Figure 6.2).

Finally, achieving the best possible therapeutic outcomes requires consideration of the following principles:

- Critical appraisal of the available evidence and its clinical applicability;
- Risk stratification and expected benefit;

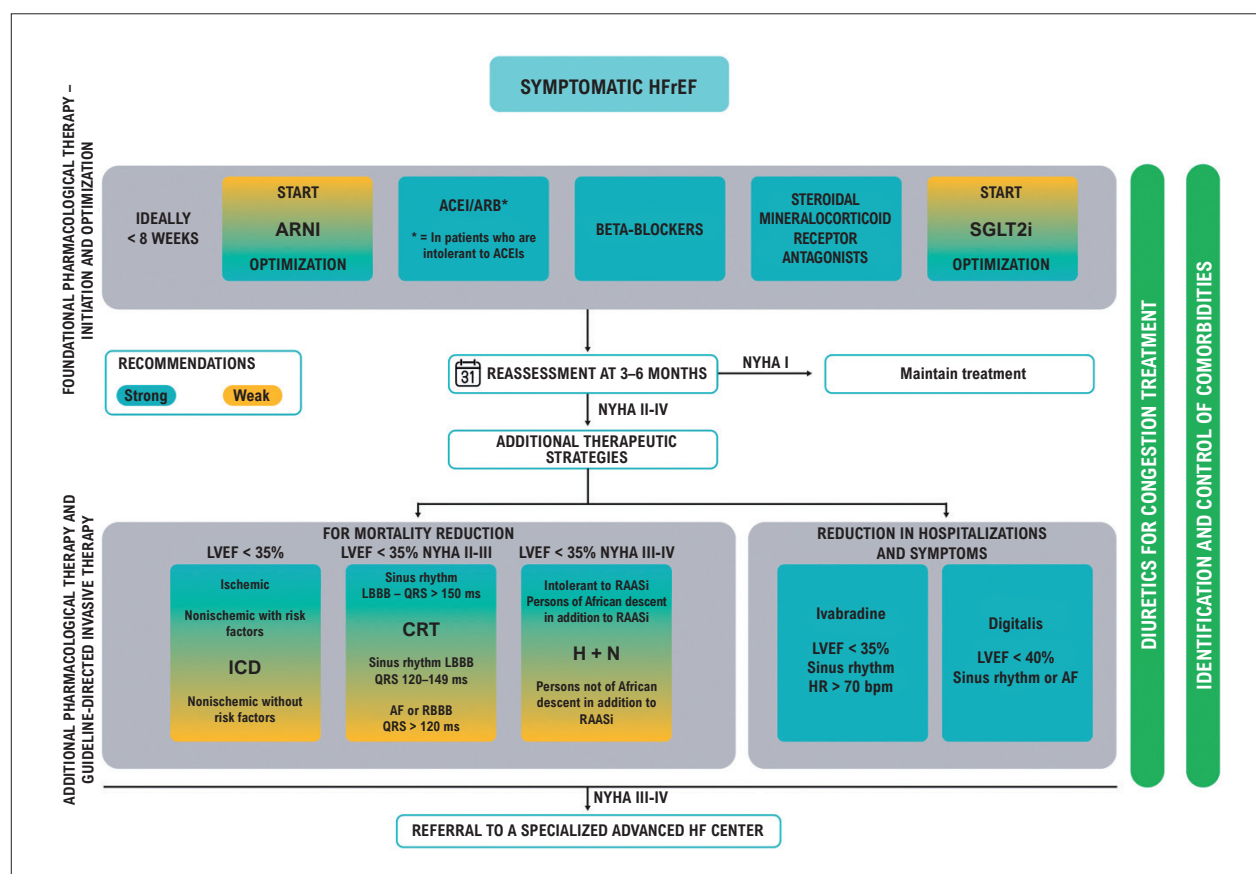


Figure 6.2 – therapeutic algorithm for symptomatic heart failure with reduced ejection fraction. ARB: angiotensin receptor blocker; RBBB: right bundle branch block; LBBB: left bundle branch block; ICD: implantable cardioverter-defibrillator; NYHA: New York Heart Association; AF: atrial fibrillation; HR: heart rate; LVEF: left ventricular ejection fraction; H+N: hydralazine plus nitrate; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; ACEI: angiotensin-converting enzyme inhibitor; ARNI: angiotensin receptor–neprilysin inhibitor; SGLT2i: sodium–glucose cotransporter 2 inhibitor; RAASi: renin–angiotensin–aldosterone system inhibitor; CRT: cardiac resynchronization therapy.

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Chart 6.1 – Initial and target doses of pharmacologic therapy for heart failure with reduced ejection fraction

Beta-blockers		
Drug	Initial dose	Target dose
Bisoprolol	1.25 mg 1x/day	10 mg 1x/day
Carvedilol	3.125 mg 2x/day	50 mg 2x/day
Metoprolol succinate	25 mg 1x/day	200 mg 1x/day

Angiotensin-converting enzyme inhibitors (ACEIs)		
Drug	Initial dose	Target dose
Captopril	6.25 mg 3x/day	50 mg 3x/day
Enalapril	2.5 mg 2x/day	10–20 mg 2x/day
Ramipril	1.25–2.5 mg 1x/day	10 mg 1x/day
Lisinopril	2.5–5 mg 1x/day	20–40 mg 1x/day
Perindopril	2 mg 1x/day	8–16 mg 1x/day

Angiotensin receptor blockers (ARBs)		
Drug	Initial dose	Target dose
Candesartan	4–8 mg 1x/day	32 mg 1x/day
Losartan	25–50 mg 1x/day	100–150 mg 1x/day
Valsartan	40–80 mg 1x/day	320 mg 1x/day

Angiotensin receptor–neprilysin inhibitors (ARNIs)		
Drug	Initial dose	Target dose
Sacubitril-valsartan	50 (24/26) mg 2x/day	200 (97/103) mg 2x/day

Aldosterone antagonists		
Drug	Initial dose	Target dose
Spironolactone	25 mg 1x/day	25–50 mg 1x/day
Eplerenone	25–50 mg 1x/day	50 mg 1x/day

Sodium–glucose cotransporter 2 (SGLT2) inhibitors		
Drug	Initial dose	Target dose
Dapagliflozin	10 mg 1x/day	10 mg 1x/day
Empagliflozin	10 mg 1x/day	10 mg 1x/day

If channel inhibitor		
Drug	Initial dose	Target dose
Ivabradin	5 mg 2x/day	7.5 mg 2x/day

Vasodilators		
Drug	Initial dose	Target dose
Hydralazine + isosorbide dinitrate	25/20 mg 3x/day	100/40 mg 3x/day

- Phenotypic profile and comorbidities, particularly frailty;
- Individualization of goals and doses;
- Avoidance of unnecessary polypharmacy whenever possible;
- Shared decision-making whenever feasible.

6.1.6. Special Considerations Regarding Cardiac Remodeling

Ventricular remodeling is a central component of the pathophysiology of HFrEF, reflecting structural and functional changes induced by neurohormonal activation. Reverse remodeling is associated with improved clinical outcomes and prognosis and represents one of the main therapeutic targets.

Conventional therapies (ACEIs, ARBs, beta-blockers, and MRAs) have demonstrated robust evidence of inducing LV reverse remodeling, with beta-blockers showing a clear dose-dependent relationship with structural improvement. In the PROVE-HF study,¹⁴⁵ treatment with an ARNI was associated with reduction in LV volumes and sustained improvement in LVEF, demonstrating consistent structural benefits. However, this was primarily a mechanistic study and was not designed to demonstrate clinical superiority.

The CATHEDRAL-HF trial evaluated patients with recovered ejection fraction who underwent gradual withdrawal of HF therapies while continuing carvedilol alone. After 1 year, no significant deterioration in LVEF or NT-proBNP was observed, suggesting that treatment withdrawal may be safe in highly selected patients. However, because of the small sample size, open-label design, and short follow-up period, its findings should be interpreted with caution and regarded as hypothesis-generating pending confirmation in larger studies.¹⁷⁸

The TRED-HF trial evaluated a distinct population of patients with idiopathic nonischemic dilated cardiomyopathy and demonstrated relapse in approximately 40% of patients following treatment withdrawal.¹⁷⁹ These findings reinforce that, in most patients, improvement in LVEF reflects functional remission rather than structural cure, especially in the presence of persistent etiologies. Thus, based on current evidence and international guidelines, continued GDMT remains the recommended strategy to preserve reverse remodeling and prevent relapse.

6.1.7. Emerging Therapies

Omecamtiv mecarbil (OM) is a selective cardiac myosin activator that enhances cardiomyocyte contractility

through direct action on the myofilaments without increasing intracellular calcium concentrations or myocardial oxygen consumption.

The GALACTIC-HF trial evaluated OM in 8256 patients with LVEF $\leq 35\%$, symptomatic HF (43% with NYHA class III), who were either hospitalized at the time of randomization or had experienced an HF hospitalization or urgent clinic visit within the previous year. After a median follow-up of 21.8 months, OM significantly reduced the primary composite outcome of HF events (worsening HF leading to treatment intensification, an urgent clinic visit, or hospitalization) or cardiovascular death (HR, 0.92; 95% CI, 0.86–0.99; $p = 0.03$).¹⁸⁰ The observed benefit was driven primarily by a reduction in HF events, without a significant reduction in cardiovascular mortality or all-cause mortality when analyzed separately.

Although the GALACTIC-HF trial confirmed the positive effect on the composite outcome, the magnitude of benefit was modest, and only a relatively small proportion of participants were receiving ARNIs or SGLT2 inhibitors. Thus, the role of OM in the era of quadruple therapy remains to be more clearly defined.

Inflammation and endothelial dysfunction in HF reduce NO production and the activation of soluble guanylate cyclase (sGC), resulting in decreased generation of cyclic guanosine monophosphate (cGMP). Vericiguat directly stimulates sGC, increasing intracellular cGMP levels. In vascular smooth muscle, this promotes vasodilation, whereas in the myocardium it exerts anti-remodeling effects without increasing myocardial oxygen demand.

The VICTORIA trial evaluated vericiguat in 5050 patients with HFrEF (LVEF $< 45\%$; mean LVEF, 29%) and evidence of recent worsening HF (hospitalization for HF within the previous 6 months or intravenous diuretic therapy within the previous 3 months). After a median follow-up of 10.8 months, vericiguat significantly reduced the primary composite outcome of cardiovascular death or HF hospitalization (HR, 0.90; 95% CI, 0.82–0.98; $p = 0.02$). Regarding safety, numerically higher rates of symptomatic hypotension (9.1% vs. 7.9%) and syncope (4.0% vs. 3.5%) were observed, without statistically significant difference.¹⁸¹

More recently, the VICTOR trial evaluated stable outpatients with HFrEF receiving optimal medical therapy and without recent clinical worsening. In this population, vericiguat did not significantly reduce the primary composite outcome (cardiovascular death or HF hospitalization), although it did demonstrate a significant reduction in cardiovascular mortality. These findings suggest the existence of mechanisms that are not yet fully understood and raise more questions than answers regarding the role of vericiguat in this patient profile.¹⁸²

Combined analyses of the VICTORIA and VICTOR trials reinforce that the benefits of vericiguat appear to be more consistent in higher-risk patients, particularly those with recent clinical worsening, in line with its current therapeutic indication.¹⁸³

6.1.8. Clinical and Laboratory Trajectory of Treatment Response in Heart Failure with Reduced Ejection Fraction

Pharmacologic therapy for HFrEF can induce reverse cardiac remodeling, characterized by reductions in LV chamber volumes and LV mass, accompanied by an increase in LVEF in a substantial proportion of patients.¹⁸⁴ Over time, it is estimated that approximately 50% of patients maintain an LVEF $\leq 40\%$, whereas about 25% transition to HFmrEF and another 25% achieve an LVEF $> 50\%$ ¹⁴ (Figure 6.3).

Treatment response can be assessed using structural, functional, and clinical parameters, including NYHA functional class, improvement in LVEF, reduction in LV dimensions, decrease in NP levels, and clinical stability. After optimal therapy, the clinical and laboratory trajectory may evolve along 3 distinct but progressive pathways within a continuum: improvement, remission, or recovery (Figure 6.3). Several factors influence the likelihood of progression along this continuum.¹⁸⁵ Among the most important is the etiology of HFrEF. Improvement in LVEF is more likely in patients with nonischemic cardiomyopathy, particularly when the precipitating insult responsible for LV dysfunction, such as myocarditis and peripartum, stress-induced, or tachycardia-induced cardiomyopathies, has resolved. Genetic factors also appear to influence this trajectory. Rare pathogenic variants in desmosomal genes and nuclear envelope genes are associated with a lower likelihood of LV reverse remodeling.¹⁸⁶ Likewise, genetic or familial etiology is associated with a lower likelihood of achieving sustained remission compared with non-genetic forms of disease.¹⁸⁷ Importantly, long-term maintenance of improved LVEF is associated with better survival. Although patients who experience improvement in LVEF generally have a more favorable prognosis than those with persistent HFrEF, the substantial risk of relapse and the lower survival compared with the general population underscore the importance of continuing optimal medical therapy.¹⁴

Besides LVEF, additional structural and functional markers contribute to prognostic stratification along this continuum. Larger LV end-diastolic diameters or volumes are associated with a greater likelihood of subsequent decline in LVEF after initial improvement.¹⁸⁸ Reduced GLS, even in patients with recovered LVEF, has been correlated with an increased risk of future events.¹⁸⁹ LGE on CMR and increased epicardial adipose tissue volume have also been associated with a lower likelihood of myocardial recovery.^{190,191}

Reductions in NP levels, particularly NT-proBNP, correlate with improvements in cardiac structure and function, with lower levels being associated with LV reverse remodeling and improvement in LVEF. A prospective observational study involving 794 patients with HFrEF using sacubitril-valsartan demonstrated a significant association between reduction in NT-proBNP and increase in LVEF.¹⁴⁵ Serial NT-proBNP measurements may serve as markers of reverse remodeling and assist in the assessment of remission and recovery. However, no specific NT-proBNP threshold has been established to define improvement in HFrEF.¹⁴

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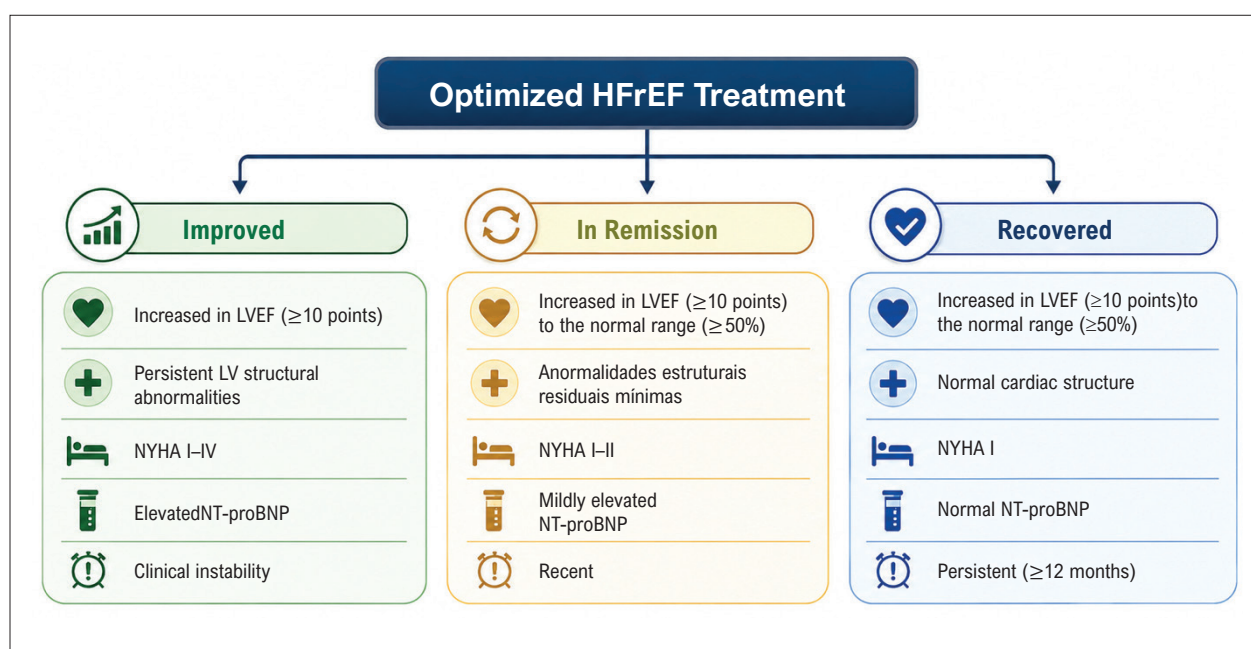


Figure 6.3 – Trajectories of left ventricular ejection fraction in response to guideline-directed medical therapy. LVEF: left ventricular ejection fraction; LV: left ventricle; NYHA: New York Heart Association; NT-proBNP: N-terminal pro-B-type natriuretic peptide. Source: adapted from Hulot et al.¹⁴

Chart 6.2 – Summary of the factors associated with the likelihood of reverse remodeling in response to treatment of heart failure with reduced ejection fraction

	Remodeling Less likely	Remodeling More likely
HF etiology	- Ischemic - Unknown	- Nonischemic - Transient myocardial injury
Genetic factors	- Pharmacogenetic variants - High-risk pathogenic genetic variants	Negative genetic testing
Comorbidities	- Atrial fibrillation - Renal dysfunction - Diabetes	- AF ablation - Normal renal function
Demographics	Older age	- Younger age - Shorter duration of HF
Pharmacologic therapy	- No use / no prescription - Discontinuation of optimal therapy	- Quadruple therapy - Good adherence

AF: atrial fibrillation; HF: heart failure.

6.1.9. Guideline-Directed Interventional Therapy for Heart Failure with Reduced Ejection Fraction

6.1.9.1. Percutaneous Treatment of Secondary Mitral Regurgitation

Secondary (functional) mitral regurgitation (MR) is a common condition in patients with HF and is associated with worsening functional status, a substantial increase in hospitalizations, and negative impact on survival.¹⁹²

The transcatheter therapy used to treat secondary MR is based on the concept of mitral transcatheter edge-to-edge repair (M-TEER), in which the free edges of the mitral valve leaflets are approximated. This technique is derived from the Alfieri mitral repair, in which the anterior and posterior leaflets are clipped together, creating a double-orifice mitral valve and thereby reducing the regurgitant volume.

The COAPT¹⁹³ and MITRA-FR⁶⁶ trials, published simultaneously in 2018, yielded conflicting results. The

COAPT trial demonstrated a clinical benefit with MitraClip implantation, whereas the MITRA-FR trial found no clinical advantage.

In the COAPT trial, 614 patients were randomly assigned to the device group (n = 302) or to the control group (n = 312). At 24 months, the annualized rate of HF hospitalizations was 35.8% per patient-year in the device group as compared with 67.9% per patient-year in the control group (HR, 0.53; 95% CI, 0.40–0.70; $p < 0.001$). All-cause mortality within 24 months occurred in 29.1% of the patients in the device group as compared with 46.1% in the control group (HR, 0.62; 95% CI, 0.46–0.82; $p < 0.001$). Thus, both outcomes favored device therapy. In this study, M-TEER was effective regardless of whether patients had previously undergone CRT or whether HF was of ischemic or nonischemic etiology. However, the greatest benefit was observed in patients with NYHA class II or III, LVEF $\leq 40\%$, and moderate-to-severe (grade 3) or severe (grade 4) MR.

The MITRA-FR trial evaluated a primary efficacy outcome consisting of a composite of all-cause mortality or unplanned hospitalization for HF at 12 months and found no significant difference between the MitraClip device group and the control group.

The RESHAPE-HF2 trial¹⁹⁴ randomly assigned 250 patients to M-TEER and 255 to medical therapy alone. At 24 months, M-TEER was significantly more effective than medical therapy in reducing the primary endpoint of recurrent HF hospitalization and the composite endpoint of cardiovascular death or recurrent HF hospitalization. In addition, patients treated with the device experienced significantly greater improvements in the KCCQ-Overall Summary (KCCQ-OS) scores at 12 months.

In this study, the device was more effective in patients who had previously undergone CRT, those with nonischemic HF, and patients with worse HF clinical and laboratory parameters, including NYHA class III or IV, LVEF $< 30\%$, hospitalization within the previous 12 months of randomization, reduced eGFR (< 50 mL/min/1.73 m²), large LV end-diastolic volume (LVEDV > 227 mL), severe (grade 4+) MR, and a large effective regurgitant orifice area (EROA > 0.27 cm²).

A recent meta-analysis¹⁹⁵ incorporating data from the 3 trials,^{66,193,194} as well as data from a RESHAPE-HF2 substudy¹⁹⁶ and the 2-year follow-up of MITRA-FR,¹⁹⁷ demonstrated that patients treated with M-TEER achieved superior outcomes compared with those receiving medical therapy alone, including:

- Lower total number of hospitalizations at 24 months (HR, 0.63; 95% CI, 0.50–0.80; $p = 0.0002$);
- Composite endpoint of first hospitalization or all-cause mortality at 24 months (HR, 0.72; 95% CI, 0.51–0.999; $p = 0.04993$);
- Change in the 6-minute walk distance (6MWD) at 12 months (32.55 m; 95% CI, 2.68–62.43; $p = 0.0327$).

In summary, the published evidence from 3 RCTs and 1 meta-analysis points toward a strong recommendation, although with moderate certainty of evidence, for the use of M-TEER in patients with severe secondary MR

and advanced LV systolic dysfunction (LVEF $< 30\%$). For patients with moderate dysfunction (LVEF 30%–40%), the recommendation also remains strong, although the certainty of evidence is lower. Therefore, M-TEER should be considered in patients with moderate-to-severe secondary MR, defined as an EROA > 0.27 cm² on echocardiography, who remain symptomatic despite optimal GDMT.

Table 6.11 summarizes the recommendations for the use of M-TEER in patients with HFrEF.

6.1.9.2. Percutaneous Treatment of Tricuspid Regurgitation

The management of TR has evolved with the introduction of tricuspid transcatheter edge-to-edge repair (T-TEER). Two devices are currently available for this approach: the TriClip (Abbott Vascular)¹⁹⁸ and the PASCAL system (Edwards Lifesciences).¹⁹⁹

The TriClip device was evaluated in the TRILUMINATE Pivotal trial, which demonstrated low complication rates and high success rates in patients treated with the device, with a significant reduction in the severity of TR from baseline.²⁰⁰ Sustained success at 1-year follow-up, compared with the control group, translated into significant improvement in clinical parameters, such as NYHA functional class, 6MWD, and KCCQ scores.²⁰⁰

The PASTE study, including 1059 patients, demonstrated that the PASCAL system achieved outcomes comparable to those of TriClip device at 1 year, with similar improvements in symptoms and quality of life.¹⁹⁹

Additional studies are needed to determine whether these devices can reduce HF hospitalizations and mortality.

More recently, the EVOQUE transcatheter tricuspid valve replacement system was evaluated in the TRISCEND II trial,²⁰¹ and the results showed that transcatheter tricuspid valve replacement was superior to medical therapy alone in improving symptoms and quality of life at 1-year follow-up. However, as with TEER, additional studies evaluating more robust clinical endpoints are needed before these therapies can be recommended in clinical practice.

6.1.9.3. Cardiac Resynchronization Therapy

6.1.9.3.1. Biventricular Cardiac Resynchronization Therapy

The efficacy of biventricular CRT has been consistently demonstrated in multiple clinical trials, with well-established benefits including improved symptoms and quality of life, reduced HF hospitalizations, and improved survival.^{202–208} These studies enrolled patients with symptomatic HF despite optimal medical therapy, severe LV systolic dysfunction (LVEF $\leq 30\%$ or $< 35\%$), and intraventricular conduction delay with a QRS duration > 120 –130 ms. Individual response to CRT, however, is variable. Several subgroup analyses of the major clinical trials have shown that 2 factors directly influence the likelihood of clinical benefits from CRT: the presence of a left bundle branch block (LBBB) pattern and QRS duration.^{61,209–211}

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Table 6.11 – Recommendations for the use of mitral transcatheter edge-to-edge repair

Recommendation	Strength of recommendation	Certainty of evidence
In patients with NYHA class II, III, or IV, severe ventricular dysfunction (LVEF < 30%), and grade 3 or 4 mitral regurgitation (EROA > 0.27 cm ²) on echocardiography who remain symptomatic despite optimal medical therapy, we recommend IN FAVOR OF M-TEER.	STRONG	MODERATE
In patients with NYHA class II, III, or IV, moderate ventricular dysfunction (LVEF 30%–40%), and grade 3 or 4 mitral regurgitation (EROA > 0.27 cm ²) on echocardiography who remain symptomatic despite optimal medical therapy, we recommend IN FAVOR OF M-TEER.	STRONG	LOW

NYHA: New York Heart Association; LVEF: left ventricular ejection fraction; EROA: effective regurgitant orifice area; M-TEER: mitral transcatheter edge-to-edge repair.

A meta-analysis of 5 landmark trials (CARE-HF, COMPANION, RAFT, MADIT-CRT, and REVERSE) found no reduction in mortality and/or HF hospitalization in patients without an LBBB morphology.²¹² Subgroup analyses from the RAFT trial suggested that patients with non-LBBB may derive limited benefit, only when the QRS duration is > 160 ms, whereas no benefit was observed in those with an intrinsic QRS duration < 150 ms, regardless of the pattern of intraventricular conduction delay.^{206,211} Clinical characteristics associated with an excellent response to CRT include nonischemic etiology, female sex, QRS duration > 150 ms, typical LBBB morphology, smaller LA volume, and body mass index (BMI) < 30 kg/m².²¹²

The benefit of CRT in patients with persistent or permanent AF may be substantially attenuated because a key determinant of CRT efficacy is the delivery of effective biventricular pacing. A substudy of the RAFT trial found no benefit of CRT without AV node ablation, as only 47% of patients had > 90% biventricular pacing.²¹³ A meta-analysis demonstrated that AV node ablation reduced mortality by 37% and nonresponse to CRT by 59% in patients with < 90% biventricular pacing, whereas no additional benefit was observed in those with > 90% biventricular pacing.²¹⁴ Although the effectiveness is limited, some patients with AF may have adequate biventricular pacing with AV nodal blocking agents (eg, beta-blockers).

Until recently, evidence supporting upgrade to CRT was limited to observational studies and registry data. The BUDAPEST-CRT Upgrade trial (n = 360) demonstrated that, in patients with a pacemaker or implantable cardioverter-defibrillator (ICD), a significant RV pacing burden, and reduced LVEF, upgrade to CRT with defibrillator (CRT-D) compared with ICD therapy alone reduced the combined risk of all-cause mortality, HF hospitalization, or absence of reverse remodeling. All-cause mortality or HF hospitalization occurred in 22 of 215 patients (10%) in the CRT-D arm vs. 46 of 145 patients (32%) in the ICD arm (HR, 0.27; 95% CI, 0.16–0.47; p < 0.001).²¹⁵

The use of CRT in patients with HF, LV systolic dysfunction, and AV block requiring pacemaker implantation is supported by at least 3 RCTs.^{216–218} In the BLOCK-HF trial, CRT significantly improved the composite outcome of LV reverse

remodeling, reduced emergency department visits or HF hospitalizations, and all-cause mortality.²¹⁸

Table 6.12 summarizes the recommendations for the use of CRT in patients with HFrEF.

6.1.9.3.2. Biventricular Cardiac Resynchronization Therapy Combined with an Implantable Cardioverter-Defibrillator

Few clinical trials have been specifically designed to directly compare biventricular CRT alone with CRT combined with an ICD. The COMPANION trial randomly assigned patients with advanced HF (NYHA class III–IV) and intraventricular conduction delay (QRS > 120 ms) to receive optimal medical therapy, biventricular CRT alone, or CRT-D; however, the primary objective of the study was to evaluate the effects of CRT compared with optimal medical therapy.²⁰⁵ The results of the COMPANION trial demonstrated that biventricular CRT compared with medical therapy significantly improved the composite outcome of all-cause mortality or hospitalization. The findings also suggested that the addition of an ICD may provide an additional survival benefit by further reducing all-cause mortality. For patients with an indication for ICD implantation, the decision to add biventricular CRT should be based on the criteria for CRT indication described above. In patients who are candidates for biventricular CRT, the decision to implant an ICD concurrently should be individualized, considering factors such as age, life expectancy, HF etiology (ischemic vs. nonischemic), coexisting comorbidities, and presence of myocardial fibrosis. In this context, the benefit of concomitant ICD therapy depends on balancing the risk of SCD against the risk of death from other noncardiovascular causes.

Table 6.13 summarizes the recommendations for the use of CRT combined with an ICD.

6.1.9.3.3. Conduction System Pacing

Although biventricular CRT is well established for reducing morbidity and mortality in patients with HFrEF and LBBB, it has limitations, including a high rate of nonresponders and high cost.

Table 6.12 – Recommendations for the use of cardiac resynchronization therapy

Recommendation	Strength of recommendation	Certainty of evidence
In patients with HF and severe ventricular dysfunction (LVEF <35%) who remain symptomatic despite optimal medical therapy at the maximum tolerated doses for at least 90 days, are in sinus rhythm, and have LBBB morphology with a QRS duration ≥ 150 ms, we recommend IN FAVOR OF biventricular CRT.	STRONG	HIGH
In patients with HF and severe ventricular dysfunction (LVEF <35%) who remain symptomatic despite optimal medical therapy at the maximum tolerated doses for at least 90 days, are in sinus rhythm, and have LBBB morphology with a QRS duration of 130–149 ms, we recommend IN FAVOR OF biventricular CRT.	WEAK	HIGH
In patients with HF and severe ventricular dysfunction (LVEF <35%) who remain symptomatic despite optimal medical therapy, are in sinus rhythm, and RBBB morphology or nonspecific intraventricular conduction delay, we recommend AGAINST biventricular CRT.	STRONG	HIGH
In patients with HF and severe ventricular dysfunction (LVEF <35%) who remain symptomatic despite optimal medical therapy at the maximum tolerated doses for at least 90 days, have atrial fibrillation and LBBB morphology, we recommend IN FAVOR OF biventricular CRT, provided that strategies are implemented to ensure an adequate rate of effective biventricular pacing (>90%).	STRONG	LOW
In patients with a conventional pacemaker or implantable cardioverter-defibrillator who subsequently develop symptomatic HF with LVEF $\leq 35\%$ despite optimal medical therapy and have a significant right ventricular pacing burden (>20%), we recommend IN FAVOR OF biventricular CRT.	STRONG	MODERATE
In patients with HF and ventricular dysfunction (LVEF $\leq 50\%$) who require ventricular pacing due to advanced atrioventricular block, we recommend IN FAVOR OF biventricular CRT to reduce morbidity.	STRONG	HIGH

HF: heart failure; LVEF: left ventricular ejection fraction; LBBB: left bundle branch block; CRT: cardiac resynchronization therapy; RBBB: right bundle branch block.

Table 6.13 – Recommendations for the Use of Cardiac Resynchronization Therapy Combined with an Implantable Cardioverter-Defibrillator

Recommendation	Strength of recommendation	Certainty of evidence
In patients who are candidates for ICD implantation and also meet the criteria for biventricular CRT, we recommend IN FAVOR OF concomitant implantation of both devices.	STRONG	HIGH
In patients who are candidates for biventricular CRT, we recommend IN FAVOR OF individualized risk assessment and shared decision-making to determine whether concomitant ICD implantation is appropriate.	STRONG	MODERATE

ICD: implantable cardioverter-defibrillator; CRT: cardiac resynchronization therapy.

Conduction system pacing (CSP) has emerged as an alternative strategy that directly recruits the His–Purkinje conduction system using a single ventricular lead, bypassing the conduction block and providing more physiological LV activation. The 2 principal CSP techniques are His bundle pacing and left bundle branch area pacing. CSP has been proposed primarily as an alternative to conventional biventricular CRT in patients who do not respond to CRT or have an unfavorable anatomy for coronary sinus lead implantation.

The safety of CSP has been consistently demonstrated in observational registries across different patient populations, with complication rates comparable to those reported for biventricular CRT.^{219–221} Small RCTs have further supported the potential efficacy of CSP. A meta-analysis of 7 RCTs comparing CSP versus biventricular CRT demonstrated a greater reduction in QRS duration (mean difference, -13 ms; 95% CI, -24 to -2 ; $p = 0.02$), greater improvement in NYHA functional class (mean difference, -0.37 ; 95% CI,

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–0.69 to –0.05; $p = 0.02$), and a more pronounced increase in LVEF (mean difference, 2.1%; 95% CI, 0.2–4.0; $p = 0.03$) in patients randomly assigned to CSP.²²² In addition, the rate of periprocedural complications was numerically lower in the CSP group. However, in contrast to earlier studies, an RCT of 179 patients conducted across the 5 geographic regions of Brazil found that CSP was inferior to biventricular CRT with respect to a hierarchical composite outcome of death, HF hospitalizations, urgent HF visits, and change in LVEF over 12 months of follow-up.²²³ Large RCTs powered to evaluate major clinical outcomes, including mortality and HF hospitalization, are currently underway.

Table 6.14 summarizes the recommendations for the use of CSP in patients with HFrEF.

6.1.9.3.4. Cardiac Contractility Modulation

Cardiac contractility modulation (CCM) is a device-based therapy that delivers electrical impulses to the RV septum during the refractory period of the cardiac cycle, with the aim of enhancing contractility without increasing myocardial oxygen consumption.²²⁴ Small RCTs, enrolling predominantly patients with HFrEF and NYHA class III, have suggested that CCM may improve functional capacity and quality of life.^{225,226} However, robust evidence demonstrating a consistent impact on major clinical outcomes, such as HF hospitalization and mortality, is still lacking.

6.1.10. Implantable Cardioverter-Defibrillator

6.1.10.1. Secondary Prevention of Sudden Cardiac Death

The use of ICDs for the secondary prevention of SCD is supported by robust evidence from large RCTs, establishing ICD therapy as the standard of care for survivors of malignant ventricular arrhythmias. The evidence is primarily derived from 3 landmark studies: the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial,²²⁷ the Canadian Implantable Defibrillator Study (CIDS),²²⁸ and the Cardiac Arrest Study Hamburg (CASH).²²⁹

Published in 1997, the AVID trial was the largest of these studies, enrolling 1016 patients who had survived cardiac arrest due to ventricular fibrillation or had experienced symptomatic sustained ventricular tachycardia. All participants had an LVEF $\leq 40\%$ and were randomly assigned to receive either an ICD or medical therapy with

amiodarone. The trial was terminated early because of the clear benefit of ICD therapy, which reduced all-cause mortality by 29%. A meta-analysis of these 3 landmark trials showed an overall 28% reduction in all-cause mortality with ICD therapy, with the greatest benefit observed in patients with LVEF $< 35\%$.²³⁰

ICD implantation might be considered in patients with syncope of unknown origin in whom hemodynamically unstable ventricular tachycardia is inducible during an electrophysiologic study (EPS), although the clinical studies supporting this recommendation are limited.

6.1.10.2. Primary Prevention of Sudden Cardiac Death

Primary prevention of SCD in patients with HFrEF has become an integral component of clinical practice over the past decades. Unlike secondary prevention, ICDs are implanted before the occurrence of any sustained ventricular arrhythmia. Several RCTs have shaped this practice, with an emphasis on stratification by LVEF and NYHA functional class.

The MADIT-I trial was the first study and investigated patients with a previous myocardial infarction, LVEF $\leq 35\%$, nonsustained ventricular tachycardia, and a positive EPS for sustained ventricular tachycardia. Participants were randomly assigned to receive either an ICD or amiodarone, and ICD therapy was associated with a 54% reduction in all-cause mortality.²³¹ The MUSTT trial reinforced the role of EPS in patients with ischemic cardiomyopathy, LVEF $\leq 40\%$, and nonsustained ventricular tachycardia. Patients treated with an ICD experienced a significant reduction in SCD (RR, 0.24; $p < 0.001$).²³² The MADIT-II simplified stratification by eliminating the requirement for nonsustained ventricular tachycardia or EPS. Patients with a previous myocardial infarction and LVEF $\leq 30\%$ were randomly assigned to receive either an ICD or standard medical therapy. ICD implantation resulted in a 31% reduction in all-cause mortality (HR, 0.69; $p = 0.016$).²³³ In contrast, the CABG Patch Trial found no benefit from prophylactic ICD implantation in patients with LVEF $\leq 35\%$ undergoing elective coronary bypass surgery.²³⁴

Two RCTs demonstrated no reduction in all-cause mortality with early ICD implantation within the first 40 days of myocardial infarction.^{235,236} Published in 2005, the SCD-HeFT trial enrolled 2521 patients with HF (ischemic or nonischemic), NYHA class II or III, and LVEF $\leq 35\%$. ICD

Table 6.14 – Recommendations for the use of conduction system pacing

Recommendation	Strength of recommendation	Certainty of evidence
In symptomatic patients with LVEF $\leq 35\%$, LBBB, and a QRS duration ≥ 150 ms receiving optimal medical therapy but in whom biventricular CRT cannot be achieved, we recommend IN FAVOR OF conduction system pacing.	STRONG	MODERATE
In patients with an indication for biventricular CRT, we recommend IN FAVOR OF conduction system pacing as an alternative pacing strategy.	WEAK	LOW

therapy was associated with a 23% reduction in all-cause mortality, making SCD-HeFT the largest trial of primary prevention.²³⁷ Finally, the DANISH trial reexamined the benefit of ICD implantation in nonischemic HF. Although all-cause mortality was not reduced, SCD occurred significantly less frequently in the ICD group (4.3% vs. 8.2%).²³⁸ Subgroup analyses by age suggested benefit in younger patients (aged < 59 years).

6.1.10.3. Patient Selection for Implantable Cardioverter-Defibrillator Therapy

Although widely used, ejection fraction has limited predictive value as the sole criterion for ICD implantation, particularly in HF of nonischemic origin. Myocardial fibrosis, assessed as LGE on CMR, has emerged as a promising marker of arrhythmic risk in observational studies. A meta-analysis of 29 studies involving nearly 3000 patients demonstrated a strong association between fibrosis and arrhythmic events.²³⁹

Recent cohort studies have suggested that myocardial fibrosis is a stronger predictor of arrhythmic risk than LVEF alone, and that a risk model integrating LGE and LVEF strata is significantly superior to LVEF alone.²⁴⁰ However, there are no randomized studies based on the presence of LGE detected by CMR. Additional risk markers include an LV end-diastolic diameter > 73 mm, the presence of periodic breathing during CPET, nonsustained ventricular tachycardia > 10 beats on Holter monitoring, and elevated NP levels.^{241,242}

Recently, genetic testing has become increasingly important in risk stratification. High-risk pathogenic variants, particularly in the lamin A/C (LMNA), phospholamban (PLN), filamin C (FLNC), desmoplakin (DSP), and RNA-binding motif protein 20 (RBM20) genes, have been associated with SCD, even in patients with LVEF > 35%. Identifying these pathogenic variants may help individualize ICD implantation decisions and guide family screening.⁵⁴

Table 6.15 summarizes the recommendations for ICD implantation

Table 6.15 – Recommendations for implantable cardioverter-defibrillator implantation

Recommendation	Strength of recommendation	Certainty of evidence
Secondary prevention		
In patients who survive cardiac arrest due to ventricular fibrillation or sustained ventricular tachycardia with severe hemodynamic instability, in the absence of a completely reversible cause, we recommend IN FAVOR OF ICD implantation for the secondary prevention of sudden cardiac death.	STRONG	HIGH
Primary prevention		
In patients with symptomatic ischemic left ventricular systolic dysfunction (LVEF ≤ 35%), NYHA class II–III, at least 40 days after myocardial infarction and 90 days after coronary bypass surgery, receiving optimal medical therapy and with good 1-year life expectancy, we recommend IN FAVOR OF ICD implantation for the primary prevention of sudden cardiac death.	STRONG	HIGH
In patients with ischemic left ventricular systolic dysfunction (LVEF ≤ 30%), NYHA class I, at least 40 days after myocardial infarction and 90 days after coronary bypass surgery, receiving optimal medical therapy and with good 1-year life expectancy, we recommend IN FAVOR OF ICD implantation for the primary prevention of sudden cardiac death.	STRONG	MODERATE
In patients with symptomatic nonischemic left ventricular systolic dysfunction (LVEF ≤ 35%), NYHA class II–III, receiving optimal medical therapy and with good 1-year life expectancy, we recommend IN FAVOR OF an individualized risk assessment to guide the decision regarding ICD implantation for the primary prevention of sudden cardiac death.	STRONG	MODERATE
In patients with symptomatic nonischemic left ventricular systolic dysfunction (LVEF ≤ 35%), NYHA class II–III, receiving optimal medical therapy and with good 1-year life expectancy, we recommend IN FAVOR OF ICD implantation for the primary prevention of sudden cardiac death when risk markers for sudden cardiac death are present.*	STRONG	MODERATE
In patients with dilated cardiomyopathy, LVEF between 36% and 50%, and a good 1-year life expectancy, we recommend IN FAVOR OF ICD implantation for the primary prevention of sudden cardiac death in the presence of high-risk arrhythmogenic genotypes together with other risk markers.*	STRONG	MODERATE

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In patients with symptomatic nonischemic left ventricular systolic dysfunction (LVEF $\leq 35\%$), NYHA class II–III, receiving optimal medical therapy and with good 1-year life expectancy, we recommend IN FAVOR OF ICD implantation for the primary prevention of sudden cardiac death regardless of individualized risk stratification.

WEAK

HIGH

In patients with a recent myocardial infarction (<40 days); or recent coronary bypass surgery (<60 days); or refractory NYHA class IV heart failure without eligibility for heart transplant, CRT, or durable mechanical circulatory support; or life expectancy <1 year, we recommend AGAINST ICD implantation for primary or secondary prevention of sudden cardiac death.

STRONG

MODERATE

**Risk markers: age <59 years, myocardial fibrosis detected by late gadolinium enhancement on cardiac magnetic resonance imaging, nonsustained ventricular tachycardia or high ventricular arrhythmic burden on Holter monitoring, and specific high-risk arrhythmogenic genotypes. ICD: implantable cardioverter-defibrillator; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; CRT: cardiac resynchronization therapy.*

6.1.10.4. Implantable Cardioverter-Defibrillator Programming

Appropriate ICD programming is essential to minimize unnecessary pacing and inappropriate shocks. For bradyarrhythmias, atrial pacing with a prolonged AV interval is preferred to avoid ventricular pacing and dyssynchrony.²⁴³ When ventricular pacing is unavoidable, CRT, physiologic pacing, or deep septal pacing might be considered.

In tachyarrhythmias, the following programming strategies are generally recommended: (1) antitachycardia pacing (ATP) before shock delivery for monomorphic ventricular tachycardia; (2) ATP during capacitor charging for ventricular fibrillation; (3) ventricular fibrillation detection thresholds > 200 bpm to initiate shock therapy; and (4) prolonged arrhythmia detection intervals to avoid inappropriate therapies. Studies such as MADIT-RIT have demonstrated that conservative ICD programming, characterized by higher rate thresholds and longer detection intervals, reduces unnecessary shocks and improves survival.²⁴⁴

6.1.10.5. Types of Implantable Cardioverter-Defibrillators

The choice of ICD system should be individualized. The main device types include:

- Conventional transvenous ICD: the most commonly used system, incorporating transvenous intracardiac leads and providing both ATP and antibradycardia pacing.
- Subcutaneous ICD (S-ICD): recommended for patients who do not require pacing, with a history of infection or difficult venous access. The S-ICD does not provide ATP.
- Extravascular ICD: an emerging technology in which the lead is positioned within the retrosternal space. This system is not currently available in Brazil.

Selection of the appropriate ICD system should consider patient age, cardiac anatomy, comorbidities, the presence of conduction abnormalities, a history of infection, and the anticipated need for ventricular pacing.

Importantly, ICD implantation should always be considered within the broader clinical context, taking into

account the patient's individual risk of SCD, life expectancy, and integration with other therapeutic strategies, including CRT, cardiac rehabilitation, and multidisciplinary team follow-up.^{245,246}

6.2. Heart Failure with Preserved Ejection Fraction

6.2.1. Introduction

HFpEF accounts for approximately 50% of all cases of HF, with a trend toward increasing prevalence relative to HFrEF. This trend is largely attributable to population aging and the growing burden of metabolic disease and hypertension, both of which are major pathophysiological drivers of the syndrome.^{63,247,248}

The annual mortality rate in patients with HFpEF is approximately 15%, increasing to as high as 26% in those who have been hospitalized. Patients experience an average of 1.4 hospitalizations per year.^{249,250}

6.2.2. Pathophysiology of Symptoms

Endothelial dysfunction, caused by chronic low-grade inflammation, is the fundamental mechanism underlying the development of HFpEF. This concept is supported by observational studies demonstrating elevated circulating levels of inflammatory biomarkers, including interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), soluble suppression of tumorigenicity 2 (sST2), and pentraxin 3 in patients with the syndrome.²⁵¹ Beyond the myocardium, endothelial dysfunction also affects the peripheral vasculature, pulmonary circulation, skeletal muscle, and kidneys.

It is important to highlight that current pathophysiological understanding recognizes HFpEF as a systemic disorder characterized by endothelial dysfunction and multiple organ involvement.²⁵² Recent evidence indicates that obesity plays a central role among the comorbidities contributing to this pathophysiological process. Dysfunctional adipose tissue promotes a systemic inflammatory milieu through altered adipokine secretion, triggering endocrine and paracrine signaling pathways that impair endothelial function. In the myocardium, these mechanisms promote increased

myocardial stiffness and adverse remodeling, contributing to LV diastolic dysfunction and creating the pathophysiological substrate responsible for the symptoms and clinical events characteristic of HFpEF.^{253,254}

6.2.3. Clinical Characteristics, Comorbidities, and Phenotypes

6.2.3.1. Clinical Characteristics

Dyspnea is the most common presenting symptom of HFpEF. Approximately two-thirds of patients exhibit signs of congestion, whereas the remaining one-third present with dyspnea in the absence of overt congestion. Comorbidities, including chronic obstructive pulmonary disease (COPD), anemia, frailty, and AF, are highly prevalent and can influence both the clinical presentation and diagnostic evaluation. Multifactorial dyspnea requires a comprehensive etiologic assessment, as appropriate treatment of HFpEF may improve clinical outcomes. Acute decompensation occurs in up to 50% of patients and is often associated with hypertension, arrhythmias, poor treatment adherence, or other stressors.⁶³

6.2.3.2. Cardiac and Noncardiac Comorbidities

The presence of CAD is associated with poor prognosis, and its early investigation should be considered. MR has emerged as an important comorbidity in HFpEF, contributing to symptom burden; in selected patients with severe disease, percutaneous intervention may be a treatment option.²⁵⁵ Chronotropic incompetence has also been described in patients with HFpEF and may be exacerbated by beta-blocker therapy, further impairing functional capacity. Pacing-induced ventricular dyssynchrony via pacemaker implantation may be associated with a decline in functional capacity and even a drop in LVEF.²⁵⁵ Hypertension is highly prevalent in HFpEF and is strongly associated with adverse outcomes. Lowering SBP to < 130 mm Hg has been associated with a reduction in HF hospitalizations.²⁵⁵

Diabetes mellitus is associated with the development of HFpEF and negatively impacts the prognosis. Obesity also plays a key pathophysiologic role by promoting neurohormonal activation, hemodynamic overload, oxidative stress, chronic low-grade inflammation, and fibrosis. The obesity-related HFpEF phenotype is now recognized as both highly prevalent and clinically important, and emerging evidence indicates that targeted treatment of obesity can improve clinical outcomes (see treatment of obesity in HFpEF). Anemia and iron deficiency also negatively impact outcomes in patients with HFpEF, although RCTs have not yet demonstrated that correction of these abnormalities improves prognosis. Even mild renal dysfunction has emerged as an important prognostic marker and is associated with disease progression. Echocardiographic studies have shown that renal dysfunction correlates with elevated ventricular filling pressures. In addition, eGFR and the presence of albuminuria have been used to identify subgroups at higher risk.²⁵⁵

Therefore, the management of comorbidities is a cornerstone of HFpEF therapy, as these conditions frequently contribute to disease progression and symptom burden. Although a detailed discussion of each comorbidity is beyond the scope of this guideline, clinicians should follow the relevant disease-specific guidelines and consensus statements to ensure optimal management.

6.2.3.3. Phenotyping of Heart Failure with Preserved Ejection Fraction

The contemporary recognition of the marked clinical heterogeneity of HFpEF has led to numerous studies using advanced statistical approaches and machine learning techniques to identify distinct phenotypic subgroups. Although different classification models have been proposed, several investigations have converged on 3 major phenotypes. Phenotype 1 comprises younger individuals with normal LV geometry and filling pressures, as well as arterial stiffness and NP levels within the normal range. Phenotype 2 consists predominantly of older women, frequently with AF. Phenotype 3 is characterized by cardiometabolic disorders, with a high comorbidity burden including an increased likelihood of obesity, diabetes, and more severe symptoms.^{256,257}

6.2.4. Mimics of Heart Failure with Preserved Ejection Fraction

Among patients with HFpEF, a subgroup has specific underlying etiologies, often related to genetic abnormalities, that consequently involve distinct pathophysiological mechanisms and potential personalized therapeutic targets. These conditions, commonly referred to as HFpEF mimics or specific phenotypes, are primarily associated with infiltrative cardiomyopathies or HCM, each with characteristic clinical manifestations and outcomes. Accordingly, clinicians should actively investigate red flags suggestive of specific etiologies in every patient with HFpEF, including clinical, ECG, and echocardiographic findings.^{258,259} Additional investigations, such as CMR, genetic testing, and, in selected cases, endomyocardial biopsy (EMB), may be required to establish an accurate etiologic diagnosis. HFpEF mimics typically present in individuals younger than 60 years, an age at which primary HFpEF is uncommon. Cardiac amyloidosis can also affect older patients, particularly the wild-type form.²⁶⁰

A thorough medical history is essential, with particular attention to family history, including premature SCD, pacemaker implantation, and HF or cardiomyopathy in younger relatives. These findings help to adequately characterize the clinical phenotype. Figure 3.3 in Chapter 3 summarizes the main cardiomyopathies that mimic HFpEF.²⁶⁰

Another condition that may resemble HFpEF is high-output HF. This syndrome may also occur in the absence of chamber dilation and is characterized by a resting cardiac output > 8 L/min or a cardiac index > 4 L/min/m². It is typically associated with increased metabolic demand, leading to higher cardiac output requirements, arteriolar vasodilation, increased venous return, greater oxygen consumption, and reduced systemic vascular resistance

(SVR).²⁶¹ The main causes of high-output HF include liver disease, arteriovenous fistulas, hyperthyroidism, thiamine deficiency, and sepsis. Recognition of these conditions is essential to avoid diagnostic errors and to ensure appropriate management.²⁵⁵

6.2.5. Diagnosis of Heart Failure with Preserved Ejection Fraction

The diagnostic algorithm for HF described in Chapter 3 can identify the majority of patients with HF. However, a subset of patients with HFpEF who do not exhibit unequivocal congestion may not be identified using that diagnostic pathway. In patients with persistent symptoms and ongoing clinical suspicion, evaluation should therefore be supplemented with HFpEF probability scores. The H₂FPEF and HFA-PEFF scores were developed and validated to estimate the likelihood of HFpEF and represent valuable tools for resolving diagnostic uncertainty.^{41,262}

A recent study using a machine learning model compared the performance of the H₂FPEF clinical score with that of the HFA-PEFF score for predicting outcomes in patients with HFpEF. The H₂FPEF score demonstrated superior diagnostic performance, with a larger area under the curve (0.845; 95% CI, 0.810–0.875) than the HFA-PEFF score (0.710; 95% CI, 0.659–0.756), corresponding to a difference of –0.134 (95% CI, –0.177 to –0.094; *p* < 0.001).³ Therefore, the H₂FPEF score is recommended as the preferred tool for the evaluation of patients with suspected HFpEF (Figure 6.4 and Chart 6.3). For patients with intermediate probability scores, diastolic stress testing, including exercise echocardiography and/or cardiac catheterization, is recommended to establish the diagnosis more accurately^{41,262} (Figure 6.4).

Novel echocardiographic parameters, particularly LA strain, have been incorporated into the 2025 American Society of Echocardiography recommendations as complementary tools for assessing diastolic function and diagnosing HFpEF.^{263,264} LA reservoir strain (LASr) reflects LA compliance and is inversely correlated with LV filling pressures, providing independent prognostic information. Furthermore, the LASr/E/e' ratio has been identified as the most robust noninvasive predictor of elevated LV filling pressures, particularly in patients with preserved ejection fraction.

Table 6.16 summarizes the recommendations for the use of probability scores in patients with suspected HFpEF

6.2.6. Pharmacologic Treatment

6.2.6.1. Sodium–Glucose Cotransporter 2 Inhibitors in Patients with Heart Failure with Preserved Ejection Fraction

SGLT2 inhibitors have been evaluated in 2 large RCTs involving patients with HFpEF and HFmrEF, ie, with LVEF > 40%. The EMPEROR-Preserved trial compared empagliflozin with placebo in patients with symptomatic HFpEF (NYHA class II–IV), structural heart disease, and NT-proBNP levels > 300 pg/mL (or > 900 pg/mL in patients with AF) or hospitalization for HF during the previous 12 months. Treatment with empagliflozin resulted in a 21% RR reduction

(RRR) in the primary composite outcome of cardiovascular death or HF hospitalization (HR, 0.79; 95% CI, 0.69–0.90). This benefit was driven primarily by a 27% reduction in HF hospitalizations (HR, 0.73; 95% CI, 0.61–0.88), whereas the reduction in cardiovascular mortality did not reach statistical significance (HR, 0.91; 95% CI, 0.76–1.09).¹⁵¹

The DELIVER trial evaluated dapagliflozin in a population that was largely comparable to that of the EMPEROR-Preserved trial. The main differences were that patients with AF were required to have NT-proBNP levels > 600 pg/mL, and an estimated creatinine clearance < 25 mL/min was an exclusion criterion, compared with < 20 mL/min in the EMPEROR-Preserved. The primary outcome was a composite of cardiovascular death or worsening HF, defined as an unplanned hospitalization or an urgent visit for DHF. Treatment with dapagliflozin demonstrated an 18% RRR in the primary outcome (HR, 0.82; 95% CI, 0.73–0.92); this benefit was likewise driven primarily by a 21% reduction in worsening HF events (HR, 0.79; 95% CI, 0.69–0.91), whereas the reduction in cardiovascular mortality was not statistically significant (HR, 0.88; 95% CI, 0.74–1.05).¹⁵¹

In addition to their primary outcomes, both trials demonstrated a significant improvement in quality of life and a reduction in NT-proBNP levels in patients treated with SGLT2 inhibitors.^{151,152,265}

Subsequent meta-analyses and systematic reviews have consistently confirmed that SGLT2 inhibitors are effective in patients with HFpEF, reducing the composite outcome of cardiovascular death or worsening HF, with the benefit being driven predominantly by a reduction in worsening HF events.^{154,266–269} In addition, another meta-analysis demonstrated improvements in health-related quality of life and functional capacity in patients with HF, regardless of ejection fraction or the presence of diabetes, further supporting the role of this drug class in patients with HFpEF.²⁷⁰

Table 6.16 summarizes the recommendations for the use of SGLT2 inhibitors in patients with HFpEF

6.2.6.2. Mineralocorticoid Receptor Antagonists

The TOPCAT trial,²⁷¹ a randomized, double-blind study, evaluated the effects of spironolactone in 3445 patients with symptomatic HF and an LVEF ≥ 45%, who were randomly assigned to receive spironolactone (15–45 mg daily) or placebo. The primary outcome was a composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of HF. After a mean follow-up of 3.3 years, spironolactone did not significantly reduce the primary outcome (HR, 0.89; 95% CI, 0.77–1.04; *p* = 0.14). However, it was associated with a reduction in HF hospitalizations (HR, 0.83; 95% CI, 0.69–0.99; *p* = 0.04). Hyperkalemia and increased serum creatinine levels were more frequent in the spironolactone group, although these laboratory abnormalities were not accompanied by an increase in clinically relevant adverse outcomes, including the need for dialysis or death from hyperkalemia. A post hoc analysis²⁷² showed treatment efficacy among patients enrolled in the Americas (HR, 0.82; 95% CI, 0.69–0.98), whereas no benefit was observed among participants

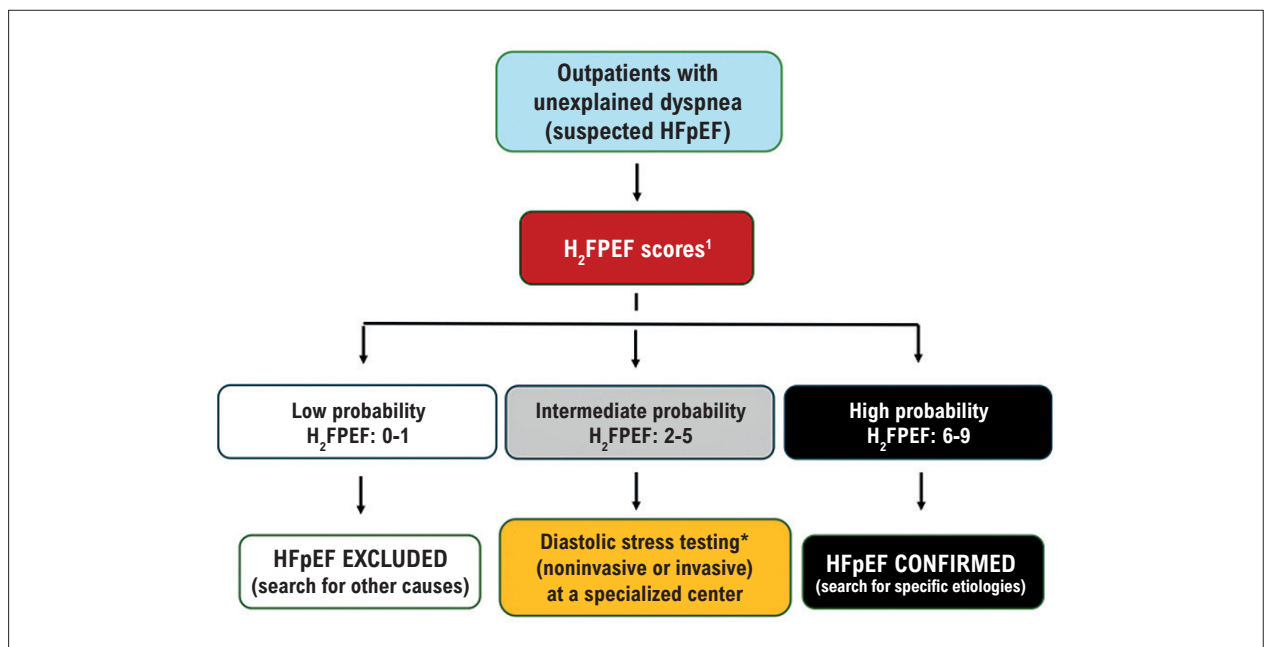


Figure 6.4 – Diagnostic algorithm for heart failure with preserved ejection fraction. *Noninvasive diastolic stress testing is performed using exercise echocardiography; invasive diastolic stress testing is performed using pulmonary artery pressure (PAP) and pulmonary capillary wedge pressure (PCWP) measurements during exercise. ¹ See Chart 6.3. HFpEF: heart failure with preserved ejection fraction; H₂FPEF: heavy, hypertensive, atrial fibrillation, pulmonary hypertension, elder, and filling pressures.

Chart 6.3 – H₂FPEF score for the diagnosis of heart failure with preserved ejection fraction

Clinical variable	Characteristics	Points
H ₂ – Obesity (Heavy)	BMI > 30 kg/m ²	2
H ₂ – Hypertension	2 or more antihypertensive medications	1
F – Atrial fibrillation	Paroxysmal or persistent	3
P – Pulmonary hypertension	PASP > 35 mm Hg (echocardiogram)	1
E – Advanced age (Elder)	Age > 60 years	1
F – Filling pressures	E/e' > 9	1

BMI: body mass index; PASP: pulmonary artery systolic pressure. Adapted from Reddy et al.⁴¹

Table 6.16 – Recommendations for the diagnosis and pharmacologic treatment of heart failure with preserved ejection fraction

Recommendation	Strength of recommendation	Certainty of evidence
In outpatients with unexplained dyspnea and suspected HFpEF, we recommend IN FAVOR OF the application of the H ₂ FPEF score to improve diagnostic accuracy.	STRONG	MODERATE
In patients with symptomatic HFpEF, we recommend IN FAVOR OF the use of an SGLT2 inhibitor (empagliflozin or dapagliflozin) to reduce the composite outcome of cardiovascular death or worsening HF.	STRONG	HIGH
In patients with symptomatic HFpEF, estimated glomerular filtration rate > 25 mL/min/1.73 m ² , and serum potassium < 5.0 mEq/L, we recommend IN FAVOR OF the use of an MRA (spironolactone or finerenone) to reduce hospitalizations and worsening HF events.	STRONG	HIGH

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In patients with HFpEF, we recommend IN FAVOR OF the use of diuretics, preferably loop diuretics, to relieve the signs/symptoms of congestion.

STRONG

LOW

In patients with symptomatic HFpEF in sinus rhythm, we recommend AGAINST the use of heart rate–lowering medications solely to achieve a target heart rate <70 bpm.

STRONG

MODERATE

HF: heart failure; HFmrEF: heart failure with mildly reduced ejection fraction; SGLT2: sodium–glucose cotransporter 2; MRA: mineralocorticoid receptor antagonist.

enrolled in Russia/Georgia (HR, 1.10; 95% CI, 0.79–1.51). In addition, another post hoc analysis¹³⁸ suggested that the potential efficacy of spironolactone was greatest at the lower end of the LVEF spectrum.

Finerenone is a nonsteroidal MRA with physicochemical properties that differ from those of steroidal MRAs, including greater receptor selectivity, a shorter half-life, and a more balanced distribution between the kidneys and myocardium. Its role in the treatment of patients with HF has been evaluated more recently.

The FINEARTS-HF trial¹³⁹ was a randomized, double-blind, placebo-controlled study that evaluated the efficacy and safety of finerenone in patients with HF and an LVEF $\geq 40\%$. The primary outcome was a composite of cardiovascular death and total worsening HF events (unplanned hospitalization or urgent visit for HF). Secondary outcomes included total HF events, NYHA functional class at 12 months, quality of life assessed by the KCCQ-Total Symptom Score (KCCQ-TSS) at 6, 9, and 12 months, a composite of renal outcomes (acute kidney injury, initiation of dialysis, or kidney transplant), and all-cause mortality. Approximately 6000 patients were randomly assigned to receive finerenone or placebo. The mean age was 72 years, 45% were women, 69% were in NYHA class II, the mean LVEF was 53%, the mean eGFR was 62 mL/min/1.73 m², 41% had diabetes, 87% were receiving loop diuretics, 70% were treated with an ACEI or ARB, and 14% were receiving an SGLT2 inhibitor. The treatment effect of finerenone was assessed in prespecified analyses according to LVEF categories (< 50%, $\geq 50\%$ to < 60%, and $\geq 60\%$) and with LVEF as a continuous variable. Among patients with HF and a preserved ejection fraction, finerenone reduced the risk of the primary composite outcome of cardiovascular death and total HF events, reduced the total number of HF events, and improved overall health status. Finerenone reduced the risk of cardiovascular death and total HF events consistently across all LVEF categories (LVEF < 50% rate ratio, 0.84 [95% CI, 0.68–1.03]; LVEF $\geq 50\%$ to < 60% rate ratio, 0.80 [95% CI, 0.66–0.97]; and LVEF $\geq 60\%$ rate ratio, 0.94 [95% CI, 0.70–1.25]; $p_{\text{interaction}} = 0.70$).²⁷³

A recent meta-analysis²⁷⁴ of 8 studies demonstrated that MRAs, including both spironolactone and finerenone, did not reduce all-cause or cardiovascular mortality but significantly lowered the risk of HF hospitalization (RR, 0.87; 95% CI, 0.77–0.89) and worsening HF events (RR, 0.83; 95% CI, 0.77–0.89) in patients with HFmrEF and HFpEF.

Table 6.16 summarizes the recommendations for the use of MRAs in patients with HFpEF.

6.2.6.3. Treatment of Obesity

Obesity predisposes individuals to HFpEF and particularly HFpEF^{275–277} especially in women.²⁷⁸ Body fat distribution appears to be more strongly associated with HFpEF than BMI.^{279,290} Obesity also complicates the diagnosis of HF. It may be the cause of dyspnea in the absence of HF and can make the physical examination more challenging, as jugular venous distention is often difficult to assess in individuals with obesity. NP levels are frequently lower in this population,^{281,282} and echocardiographic markers of congestion are underestimated.^{282,283} Patients with obesity tolerate decongestion less well and experience WRF.²⁸⁴

Small RCTs have demonstrated that, among older adults with obesity and HFpEF, caloric restriction and aerobic exercise training significantly improve functional capacity (peak VO₂) and quality of life. The addition of resistance training did not provide further improvement in these outcomes.^{285–287} Retrospective cohort studies have shown that bariatric surgery is associated with reductions in HF hospitalization and cardiovascular mortality.^{288–293} The glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide did not demonstrate clinical benefit in patients with HF, and uncertainties remain regarding its safety in this population.^{294,295}

The STEP-HFpEF trial randomly assigned 529 patients with HFpEF and BMI ≥ 30 kg/m² to receive once-weekly semaglutide (2.4 mg) or placebo for 52 weeks. Compared with placebo, semaglutide produced an improvement in the KCCQ-CSS, with a mean between-group difference of 7.8 points (16.6 vs. 8.7 points; 95% CI, 4.8–10.9; $p < 0.001$). Mean weight loss was 13.3% with semaglutide compared with 2.6% with placebo (estimated mean difference, –10.7%; 95% CI, –11.9 to –9.4; $p < 0.001$). The mean change in the 6MWD was 21.5 m with semaglutide and 1.2 m with placebo (mean difference, 20.3 m; 95% CI, 8.6–32.1; $p < 0.001$). The decrease in the hs-CRP level was significantly more pronounced with semaglutide, while serious adverse events occurred more frequently in the placebo group.²⁹⁶ The results were consistent for LVEF 45%–49%, 50%–59%, and $\geq 60\%$.^{154,297}

The STEP-HFpEF DM trial randomly assigned 616 patients with HFpEF, BMI ≥ 30 kg/m², and type 2 diabetes mellitus to receive semaglutide or placebo, yielding similar results. Semaglutide improved KCCQ-CSS (13.7 vs. 6.4 points; mean difference, 7.3 points; 95% CI, 4.1–10.4; $p < 0.001$) and produced greater weight loss (–9.8% vs. –3.4%; estimated difference, –6.4%; 95% CI, –7.6 to –5.2; $p < 0.001$).²⁹⁸ A post hoc pooled analysis of 4 RCTs comparing semaglutide with placebo included 22,282

participants, of whom 3743 had HFpEF. In this subgroup, semaglutide reduced the risk of the composite outcome of cardiovascular death or worsening HF events (5.4% vs. 7.5%; HR, 0.69; 95% CI, 0.53–0.89; $p = 0.0045$) and of worsening HF events alone (2.8% vs. 4.7%; HR, 0.59; 95% CI, 0.41–0.82; $p = 0.0019$). No significant effect on cardiovascular death alone was observed. A lower proportion of patients treated with semaglutide had serious adverse safety events, although this difference did not reach statistical significance.²⁹⁹ It should be noted, however, that this analysis included data from the SELECT and FLOW trials, which were not specifically designed to evaluate HF outcomes and may therefore introduce bias.

The SUMMIT trial compared tirzepatide – a long-acting agonist of glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors – with placebo in 731 patients with HF, LVEF $\geq 50\%$, and BMI ≥ 30 kg/m², treated for at least 52 weeks. The composite outcome of cardiovascular death or worsening HF events occurred in 9.9% of patients receiving tirzepatide and 15.3% of those receiving placebo (HR, 0.62; 95% CI, 0.41–0.95; $p = 0.026$), with the benefit driven primarily by a reduction in worsening HF events. The mean (SD) change in the KCCQ-CSS was 19.5 (1.2) in the tirzepatide group and 12.7 (1.3) in the placebo group (between-group difference, 6.9; 95% CI, 3.3–10.6; $p < 0.001$). Tirzepatide significantly decreased body weight (–13.9% [0.4%] vs. –2.2% [0.5%]; $p < 0.001$) and hs-CRP levels (–38.8% [4.5%] vs. –5.9% [5.3%]; $p < 0.001$), with a mean increase of 18.3 min in the 6MWD (95% CI, 9.9–26.7; $p < 0.001$). In addition, tirzepatide reduced the risk of worsening HF events requiring hospitalization or the use of intravenous medications in an urgent care setting (HR, 0.41; 95% CI, 0.22–0.75; $p = 0.004$).^{300,301}

Table 6.17 summarizes the recommendations for the treatment of obesity in patients with HFpEF

6.2.6.4. Other Drugs in the Treatment of Heart Failure with Preserved Ejection Fraction: Angiotensin II Receptor Blockers, Angiotensin Receptor–Neprilysin Inhibitors, and Beta-blockers

RCTs evaluating ACEIs and ARBs have not demonstrated a reduction in major clinical outcomes in patients with HFpEF.^{302,303} In a subgroup analysis of the CHARM program, candesartan did not reduce the composite outcome of cardiovascular death or HF hospitalization in patients with LVEF $\geq 50\%$ (HR, 0.95; 95% CI, 0.79–1.14).¹⁶¹ Consistently, a Cochrane systematic review found no association between ACEI or ARB therapy and reductions in cardiovascular mortality, HF hospitalization, or improvement in quality of life.³⁰⁴

A pooled analysis of the PARAGON-HF and PARADIGM-HF trials suggested that sacubitril-valsartan has a neutral effect on HF-related outcomes in patients with higher LVEF.¹⁴¹ A network meta-analysis including the PARAMOUNT-HF and PARAGON-HF trials found that sacubitril-valsartan did not reduce the composite outcome of cardiovascular death or HF hospitalization compared with valsartan in patients with HFpEF (HR, 0.89; 95% CI, 0.66–1.20).¹⁴² Another pooled analysis of the PARAGLIDE-HF and PARAGON-HF trials showed that, among patients with LVEF $> 60\%$, sacubitril-valsartan also had a neutral effect (RR, 1.09; 95% CI, 0.86–1.40).³⁰⁵ Furthermore, a cost-effectiveness analysis indicated that the addition of an ARNI to an MRA and an SGLT2 inhibitor provides low economic value from a U.S. public health care sector perspective.³⁰⁶ Given these findings and the clinical heterogeneity of HFpEF, robust evidence is lacking to support a recommendation for the use of sacubitril-valsartan in this population.

A meta-analysis of RCTs found that beta-blockers did not significantly reduce the risk of death or cardiovascular hospitalization in patients with HFpEF (HR, 0.66; 95% CI, 0.38–1.15).¹³³ However, only 1 trial evaluating nebivolol contributed data to the HFpEF subgroup. In a multicenter RCT including a small sample of patients, beta-blocker withdrawal

Table 6.17 – Recommendations for the treatment of obesity in patients with heart failure with preserved ejection fraction

Recommendation	Strength of recommendation	Certainty of evidence
In patients with HFpEF, we recommend IN FAVOR OF caloric restriction and regular exercise training to improve functional capacity (peak VO ₂) and quality of life.	STRONG	MODERATE
In patients with HFpEF and obesity (BMI ≥ 30 kg/m ²), we recommend IN FAVOR OF the use of tirzepatide to decrease body weight, improve quality of life, and reduce the composite outcome of worsening HF events* or cardiovascular death.	STRONG	MODERATE
In patients with HFpEF and obesity (BMI ≥ 30 kg/m ²), we recommend IN FAVOR OF the use of semaglutide to decrease body weight and improve quality of life and functional capacity.	STRONG	MODERATE
In patients with HFpEF and obesity (BMI ≥ 30 kg/m ²), we recommend IN FAVOR OF the use of semaglutide to reduce the composite outcome of cardiovascular death or worsening HF events.	WEAK	LOW

*Worsening HF events include hospitalization or an urgent visit requiring intravenous medications. HF: heart failure; HFpEF: heart failure with preserved ejection fraction; BMI: body mass index.

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in patients with HFpEF was associated with a significant improvement in functional capacity, as measured by peak VO_2 .³⁰⁷ However, this finding requires confirmation in MRCT trials with larger patient samples. Therefore, the present panel concludes that the available evidence is insufficient to recommend the use or systematic withdrawal of beta-blockers in patients with HFpEF.

6.2.6.5. Management of Hypervolemia

Management of circulatory congestion follows the same principles discussed in section 6.1.4.1 and should be performed preferentially with loop diuretics.⁶³

Table 6.16 summarizes the recommendations for the use of loop diuretics in patients with HFpEF.

6.2.6.6. Blood Pressure Control

Hypertension plays a key role in the pathophysiology of HFpEF, and adequate BP control is essential for symptom management. However, no specific antihypertensive strategy has been tested in dedicated RCTs in HFpEF.³⁰⁸ Current recommendations are derived from subgroup analyses rather than from studies specifically designed for patients with HF.³⁰⁹

Some studies support titration of antihypertensive therapy to achieve an SBP < 130 mmHg in patients with HFpEF. This recommendation is based on evidence that more intensive BP control is associated with a significant reduction in cardiovascular outcomes among individuals at high cardiovascular risk, although it may also increase the risk of renal dysfunction.^{309,310}

The SPRINT trial demonstrated that intensive BP control significantly reduced the incidence of HF and cardiovascular events in patients at high cardiovascular risk.³¹¹ Furthermore, a pooled analysis of the I-PRESERVE, TOPCAT, PARAGON-HF, and DELIVER trials identified a J-shaped relationship between SBP and cardiovascular risk, with the lowest risk observed at SBP levels between 120 and 130 mmHg. These findings suggest that maintaining SBP within this range may benefit

patients.³¹² Pharmacologic strategies for BP control in HFpEF commonly include RAAS inhibitors, although these agents have not demonstrated clear superiority in HFpEF-specific clinical trials. MRAs and ARNIs may also be considered, particularly in patients with resistant hypertension. SGLT2 inhibitors represent another therapeutic option that may contribute to BP control while providing additional cardiovascular benefits.

In clinical practice, the management of hypertension generally involves a combination of antihypertensive agents tailored to each patient's clinical profile and comorbidities.^{313,314}

6.2.6.7. Rate Control

Aggressive HR reduction leading to bradycardia should be avoided in patients with HFpEF because of its potential adverse effects on stroke volume and exercise tolerance.^{313,314}

Beta-blockers may exacerbate chronotropic incompetence, defined as an impaired ability to increase HR during exercise, thereby worsening exercise intolerance, one of the hallmark symptoms of HFpEF.^{313,314} A meta-analysis of RCTs found no significant improvement in exercise capacity or HF severity with beta-blocker therapy in HFpEF, although these agents may still provide benefit in patients with concomitant CAD or AF.³¹⁵ Ivabradine has also been evaluated in RCTs for rate control in patients with HFpEF in sinus rhythm; however, it failed to demonstrate clinical benefit, and the trial was terminated early.³¹⁶ Nondihydropyridine calcium channel blockers (CCBs), such as diltiazem and verapamil, may also be used for rate control but should be prescribed with caution because of their myocardial depressant effects, which may further impair stroke volume and exercise tolerance.³¹⁷

Table 6.16 summarizes the recommendations for rate control in patients with HFpEF.

6.2.7. Overview of the Management of Heart Failure with Preserved Ejection Fraction

Figure 6.5 summarizes the pharmacologic therapies recommended for the management of HFpEF.

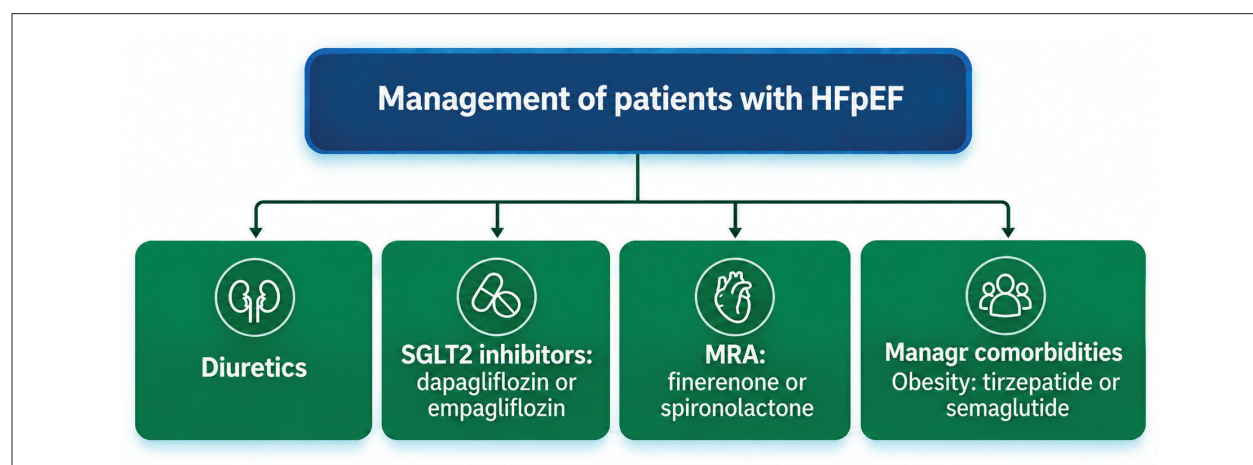


Figure 6.5 – Pharmacologic management of HFpEF. LVEF: left ventricular ejection fraction; SGLT2i: sodium–glucose cotransporter 2 inhibitor; MRA, mineralocorticoid receptor antagonist.

6.3. Nonpharmacologic and Multidisciplinary Treatment

6.3.1. Multidisciplinary Care Programs

Over the past 3 decades, robust evidence from RCTs has established multidisciplinary HF management programs as an essential adjunct to pharmacologic treatment, particularly through educational interventions that promote patient self-care.³¹⁸

A cornerstone of these programs is the multidisciplinary care approach, which emphasizes patient education during hospitalization, especially throughout discharge planning and the transition to home, as well as in the outpatient setting.³¹⁹ This approach includes education on HF, prognosis and treatment, active self-care behaviors to recognize and manage signs and symptoms of decompensation, weight management, medication adherence, nutritional counseling, and structured exercise programs.³¹⁸ The implementation of a multidisciplinary HF management program should be tailored to the local health care system, taking into account available infrastructure, facilities, human resources, and financial resources. Physicians and nurses with expertise in HF, together with primary care physicians, constitute the core multidisciplinary team. The participation of other health care professionals, including dietitians, physical therapists, pharmacists, exercise physiologists, psychologists, and social workers, is strongly recommended to provide comprehensive patient care.

6.3.2. Patient Education, Self-Care, and Lifestyle Counseling

Patient education about HF and the development of daily self-care skills are considered the cornerstone of nonpharmacologic management and the key component of multidisciplinary care programs.^{318,320}

Self-care encompasses a range of behaviors aimed at maintaining healthy lifestyle choices, recognizing symptoms of DHF, and making appropriate decisions in response to the onset of these manifestations.³²¹

For patients hospitalized for DHF, identifying the precipitating cause is essential, and, as soon as clinically feasible, education on self-care and the identification of individual vulnerabilities should be initiated. A recent RCT demonstrated that the teach-back method has a positive impact on self-care maintenance, symptom perception, and self-care management and efficacy.³²² The HELLEN-II trial evaluated the effectiveness of a nurse-led management program based on face-to-face education and follow-up over

180 days after a recent HF hospitalization. The combination of home visits and telephone reinforcement resulted in a 27% reduction in the composite outcome of hospital readmissions, emergency department visits, and all-cause mortality during the first 6 months of follow-up.³²³

Based on this high level of evidence, patients recently hospitalized for HF should be followed in dedicated HF clinics or multidisciplinary HF management programs, particularly those at high risk of readmission. A telephone contact within the first 5 days of discharge to review medications and reinforce educational messages is considered highly important, followed by a scheduled outpatient visit 7 to 14 days after hospital discharge.^{4,324}

Table 6.18 summarizes the recommendations for multidisciplinary HF management programs.

6.3.3. Sodium Restriction

Limiting excessive sodium intake is an important component of the nonpharmacologic management of HF. However, the optimal level of sodium intake for patients with HF remains controversial. For many years, a low-sodium diet, ideally corresponding to an intake of up to 4 g of sodium chloride (table salt) per day, was routinely recommended.³²⁴⁻³²⁶ However, some studies have suggested that overly restrictive sodium diets may initiate neurohormonal activation and contribute to DHF.³²⁶

More recent studies have shown that a moderate sodium restriction (2–3 g of salt per day) is associated with greater improvements in survival and quality of life than a highly restrictive diet (< 2 g of salt per day), which has not been associated with reductions in hospitalization or mortality.³²⁷

Therefore, very low-sodium diets have not demonstrated clinical benefit and may even contribute to malnutrition and cachexia.³²⁸ Furthermore, they have not been shown to improve rates of rehospitalization, quality of life, or mortality.^{4,329}

Conversely, normal-sodium diets (approximately 6–7 g of salt per day) are generally more palatable, promoting better nutritional intake without adversely affecting disease progression.³³⁰

Nevertheless, patients should be advised to avoid processed foods, which are typically high in sodium and other additives that may precipitate HF decompensation and increase the risk of hospitalization.

Table 6.19 summarizes the recommendations for sodium intake in patients with HF

Table 6.18 – Recommendations for multidisciplinary heart failure management programs

Recommendation	Strength of recommendation	Certainty of evidence
In patients with heart failure, we recommend IN FAVOR OF participation in multidisciplinary care programs to improve treatment adherence, promote self-care, enhance quality of life, and reduce hospitalizations, mortality, and hospital costs.	STRONG	MODERATE

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Table 6.19 – Recommendations for sodium intake in patients with heart failure

Recommendation	Strength of recommendation	Certainty of evidence
We recommend IN FAVOR OF avoiding excessive salt intake (>7 g of salt per day).	STRONG	MODERATE
In stable outpatients with heart failure, we recommend AGAINST a highly restrictive low-salt diet (<2 g of salt per day).	STRONG	MODERATE

6.3.4. Fluid Restriction

There is still limited evidence defining the optimal daily fluid intake for outpatients with chronic HF.

Patients with clinical instability, persistent symptoms, or multiple hospitalizations may be advised to restrict fluid intake to 1000–1500 mL/day.³³¹

For patients with chronic stable HF,³³² a fluid restriction of up to 2000 mL/day or intake according to thirst does not appear to influence rates of HF rehospitalization or mortality.³³³ Moreover, studies suggest that liberal fluid intake may be beneficial in patients with stable body weight.³³⁴ A recent study compared 2 groups of stable patients without a history of hospitalization, receiving optimal GDMT and classified as NYHA class II. One group received advice for fluid restriction (1500 mL/day), whereas the other received advice for liberal fluid intake. Patients in the latter group reported significantly less thirst distress, with no increase in adverse events.³³⁵

Therefore, fluid restriction is not required for patients with chronic stable HF. Fluid intake should be individualized according to the stage of the natural history of HF and associated comorbidities.

Table 6.20 summarizes the recommendations for fluid intake in patients with HF.

6.3.5. Cardiac Rehabilitation in Heart Failure

Cardiac rehabilitation is a structured intervention designed to improve patients' overall health and quality of life. In patients with HF, participation should begin after a comprehensive medical evaluation and include a combination of exercise training, multidisciplinary counseling to reduce stress and promote physical and mental well-being, and education on healthy lifestyle habits.

Regular physical activity is recommended for patients with stable HF by most major cardiology societies worldwide.

Cardiac rehabilitation programs may incorporate a variety of exercise modalities, including moderate-intensity continuous aerobic training, high- and low-intensity interval training, resistance training, and respiratory muscle training (Figure 6.6). These interventions should be accompanied by standardized protocols for clinical and cardiology follow-up, with objective assessment of functional, psychological, nutritional, and social outcomes. Despite the multiple benefits of cardiac rehabilitation in HF, participation in exercise programs remains suboptimal because of psychosocial, economic, logistical, and referral-related barriers. A promising alternative is home-based rehabilitation with remote supervision through mobile applications and telemetry, after a period of evaluation and supervised training in specialized centers.

Recent systematic reviews and meta-analyses of RCTs published in 2023, including 51 studies of patients with HFrEF and 9 studies of patients with HFpEF (Cochrane Library: 60 studies involving 8728 participants),³³⁶ demonstrated that structured exercise programs, compared with a non-exercise control group, reduced all-cause hospitalization (RR, 0.69; 95% CI, 0.56–0.86) and improved quality of life (mean difference, –7.39; 95% CI, –10.30 to –4.47), regardless of whether rehabilitation was center-based, home-based, or hybrid. No significant differences were observed in all-cause or cardiovascular mortality (RR, 0.87; 95% CI, 0.71–1.21). The minimum follow-up was 6 months.

A more recent systematic review, including 72 RCTs and 8495 participants, showed a 20% reduction in all-cause hospitalization (RR, 0.80; 95% CI, 0.70–0.92) and improvement in functional capacity (RR, 3.31; 95% CI, 2.22–4.15), without an impact on all-cause mortality (RR, 0.90; 95% CI, 0.79–1.03; $p = 0.904$) or quality of life (RR, 0.79; 95% CI, 0.49–1.09).³³⁷

A critical issue is adherence to rehabilitation programs. In the HF-ACTION trial, the largest trial involving patients with HFrEF, medium- and long-term adherence was 65%.³³⁸

Table 6.20 – Recommendation on fluid intake in patients with heart failure

Recommendation	Strength of recommendation	Certainty of evidence
In clinically stable patients with HF receiving optimal medical therapy who are asymptomatic or have only mild symptoms (NYHA class I–II), we recommend AGAINST strict fluid restriction (<1500 mL/day).	STRONG	LOW

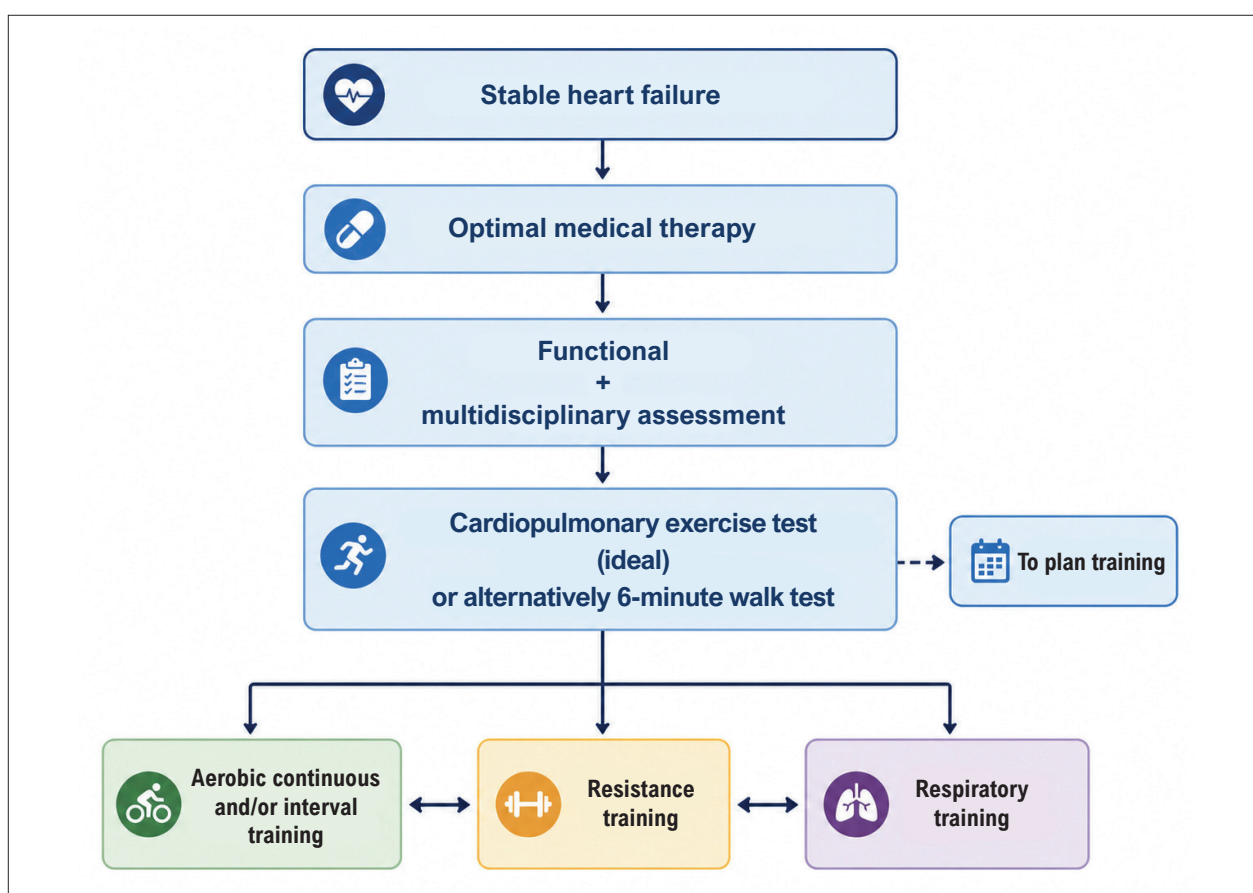


Figure 6.6 – Algorithm illustrating the indication of cardiac rehabilitation in patients with heart failure, including baseline functional assessment to guide exercise prescription.

The ExtraMATCH II meta-analysis reported a medium- and long-term adherence rate of only 38%.³³⁹ Although, to date, there is no robust evidence demonstrating a mortality benefit of cardiac rehabilitation in HF, particularly after 6 months of continuous participation, cardiac rehabilitation effectively reduces hospitalization rates, improves exercise tolerance through functional gains, and substantially improves quality of life in patients with both HFrEF and HFpEF.

Table 6.21 summarizes the recommendations for exercise training and cardiac rehabilitation in patients with HF.

6.3.6. Occupational Activity

Patients should be encouraged to remain professionally active whenever their work does not provoke significant HF symptoms. In addition to its financial benefits, employment plays an important role in maintaining social engagement, emotional well-being, and self-esteem. However, occupational activities should not contribute to disease progression or worsening of symptoms.³⁴⁰ When a patient's job involves substantial physical exertion, a change in work duties should be considered on an individual basis after optimization of both pharmacologic and nonpharmacologic treatment.

Special circumstances (eg, occupations considered high risk and/or patients with ICDs) require individualized assessment.¹

6.3.7. Sexual Activity

As with any form of aerobic exercise, sexual activity should be limited by the presence of symptoms. Erectile dysfunction is common in patients with HF and may be associated with multiple factors, including adverse effects of medications (diuretics and beta-blockers) and comorbid organ dysfunction (diabetes mellitus). Patients should receive counseling on maintaining a healthy sexual life, including psychological support, strategies to reduce physical exertion during sexual activity, and medications for erectile dysfunction, such as phosphodiesterase type 5 (PDE5) inhibitors (sildenafil and tadalafil). Systematic reviews and meta-analyses of RCTs evaluating the efficacy and safety of sildenafil in patients with HF have shown that PDE-5 inhibition improves functional capacity and may reduce hospitalizations.³⁴¹ In addition, sildenafil has been shown to be safe for the treatment of erectile dysfunction⁵ in patients with HF.³⁴²

6.3.8. Smoking and Illicit Drug Use

Smoking increases the risk of pulmonary infections and HF by increasing the risk of CAD.³⁴³ Studies have demonstrated

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Table 6.21 – Recommendations for exercise training and cardiac rehabilitation in patients with heart failure

Recommendation	Strength of recommendation	Certainty of evidence
In patients with stable HFrEF or HFpEF, we recommend IN FAVOR OF regular exercise training to improve functional capacity, alleviate symptoms, enhance quality of life, and reduce the risk of hospitalization.	STRONG	MODERATE
In patients with HF, with or without noninvasive ventilation, we recommend IN FAVOR OF low-intensity exercise training during hospitalization once clinical stabilization has been achieved.	WEAK	LOW
In patients with clinically unstable HF, acute myocarditis, or acute systemic infectious processes, we recommend AGAINST exercise training.	STRONG	MODERATE

HF: heart failure; HFrEF: heart failure with reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction.

that smoking cessation reduces the incidence of serious adverse events, including myocardial infarction, HF, stroke, and death. All patients with HF should be encouraged to quit smoking and receive counseling aimed at complete tobacco cessation, preferably through specialized smoking cessation programs. Nicotine replacement therapy and pharmacologic interventions for smoking cessation may be used in accordance with established clinical recommendations.^{344,345}

Regarding illicit drugs, complete abstinence is recommended without exception.³⁴⁶

6.3.9. Alcohol Consumption

Alcohol may act as an etiologic agent of cardiomyopathy and can also contribute to episodes of DHF by impairing myocardial contractility and precipitating cardiac arrhythmias. In addition, some patients temporarily discontinue their prescribed medications during periods of alcohol consumption, a behavior that may contribute to worsening HF. For patients with alcoholic cardiomyopathy, complete abstinence from alcohol is strongly recommended.³⁴⁴

6.3.10. Vaccination

Current evidence indicates that episodes of viral or bacterial infection are followed by a substantial increase in the risk of cardiovascular events, including myocardial infarction, stroke, and hospitalization for DHF. Vaccination prevents potentially severe diseases, hospitalizations, sequelae, and death, protects against the decompensation of chronic diseases triggered by infections, and reduces the risk of cardiovascular and cerebrovascular events.

6.3.10.1. Impact of Infections on Patients with Heart Failure

Viral and bacterial infections can trigger inflammatory and immune responses that lead to complications such as myocarditis, worsening myocardial function, atherosclerotic plaque destabilization, and consequently ischemic events or, depending on the pathogen, thromboembolic events. Systemic inflammation promotes the release of pro-inflammatory cytokines, including IL-6 and TNF- α .

Elevated levels of these inflammatory mediators can lead to depressed myocardial contractility, which may explain HF destabilization.

The Atherosclerosis Risk in Communities (ARIC) study, which included 451,588 adults aged 35 to 84 years, demonstrated not only an increase in hospitalizations for myocardial infarction but also a marked increase in hospitalizations for DHF.³⁴⁵

Respiratory syncytial virus (RSV) infection, in particular, has been associated with a substantial increase in the risk of cardiovascular events. Among 6248 adults aged ≥ 50 years hospitalized for RSV infection during the 2014–2015, 2017–2018, and 2022–2023 RSV seasons, the rate of any cardiovascular event was 22% and of DHF, 16%. Patients with HF are particularly vulnerable to RSV-associated complications. In one series, 2042 adults with HF evaluated between 2015 and 2017 experienced an 8-fold higher rate of RSV-associated hospitalization than adults without HF, with hospitalization risk increasing with age.³⁴⁶ Among patients aged ≥ 60 years, all-cause mortality within 12 days of hospital admission was approximately 20%; in patients with HF, mortality approached 30%, and among those with DHF during hospitalization, mortality increased to approximately 45%.³⁴⁷

Viral infections are the leading cause of myocarditis, although their prevalence varies according to the causative pathogen. The most frequently implicated viruses include enteroviruses (especially coxsackievirus B), adenoviruses, parvovirus B19, herpesviruses, cytomegalovirus, Epstein–Barr virus, hepatitis C virus, influenza virus, HIV, and, more recently, SARS-CoV-2.³⁴⁸

6.3.10.2. Influenza Vaccination

A retrospective analysis of the Danish Nationwide Cohort Study involving patients with HF demonstrated that influenza vaccination was associated with reductions in both all-cause and cardiovascular mortality. Patients who received influenza vaccination during more than 3 consecutive influenza seasons experienced a 29% reduction in the risk of cardiovascular death.³⁴⁹ Of note, this magnitude of benefit is comparable to that observed with established disease-modifying HF therapies, such as beta-blockers and RAAS inhibitors.

The benefits of influenza vaccination appear to be particularly pronounced in patients aged > 70 years.³⁵⁰

In a prospective analysis of 5129 patients with HF assigned to receive either influenza vaccination or placebo, with clinical events assessed every 6 months between 2015 and 2021, influenza vaccination during influenza seasons was associated with a 21% reduction in all-cause mortality, a 27% reduction in cardiovascular mortality, and a lower incidence of pneumonia.³⁵¹

A robust analysis was conducted in the FLUNITY-HD trial,³⁵² which analyzed data from 466,320 individuals randomly assigned to receive either a high-dose influenza vaccine (containing 4 times the standard antigen concentration) or a standard-dose influenza vaccine. The high-dose vaccine was associated with a significantly lower rate of hospitalization for cardiovascular disease (6.6%; $p = 0.010$) and was particularly effective in reducing HF hospitalizations, with a relative vaccine effectiveness of 21.3% ($p = 0.003$).

Therefore, annual influenza vaccination is recommended for patients with HF, especially the high-dose vaccine.

6.3.10.3. Pneumococcal Vaccination

Pneumococcal vaccination is recommended for all patients with heart disease, regardless of age, and may be administered either as a single dose of the 20-valent pneumococcal conjugate vaccine (PCV20) or as a sequential schedule consisting of the 15-valent (PCV15) or 13-valent (PCV13) vaccine, followed by the 23-valent pneumococcal polysaccharide vaccine (PPSV23) 6 to 12 months later.

6.3.10.4. COVID-19 Vaccination

During the COVID-19 pandemic, cases of vaccine-associated myocarditis were reported, particularly following messenger RNA (mRNA)-based vaccines, occurring predominantly in male adolescents and young adults.³⁵³

The occurrence of myocarditis after COVID-19 vaccination has been estimated at only 4–12 cases per million vaccinated individuals, whereas COVID-19 infection has been associated with 40–450 cases of myocarditis per million individuals, ie, the risk of COVID-19-related myocarditis

is 16 to 40 times higher than that of COVID-19 vaccine-associated myocarditis.^{354–356}

Importantly, vaccine-associated myocarditis has consistently been described as mild, with rapid clinical resolution and an excellent prognosis, in contrast to myocarditis secondary to SARS-CoV-2 infection. Therefore, COVID-19 vaccination should be administered every 6 months using the most up-to-date vaccine formulation available.

6.3.10.5. Respiratory Syncytial Virus Vaccination

A single dose of the RSV vaccine is recommended for all adults aged ≥ 70 years and for adults aged ≥ 60 years with underlying medical conditions, including heart disease.

6.3.10.6. Other Vaccinations

The herpes zoster vaccine is recommended for all adults aged ≥ 50 years, administered as a 2-dose series with an interval of 2 to 6 months between doses.

The adult tetanus, diphtheria, and acellular pertussis vaccine (Tdap) is recommended for all adults, with booster doses every 10 years.

The hepatitis B vaccine should be administered to susceptible older adults who have not been previously vaccinated, using the standard 3-dose schedule.

Because of the increased risk of serious adverse events in adults aged > 60 years, yellow fever vaccination should be considered on an individual basis.

Table 6.22 summarizes the vaccination recommendations for patients with HF.³⁵⁷

6.3.11. Family Planning

Family planning is an essential component of care for patients with HF and should include pregnancy risk stratification, selection of the most appropriate contraceptive method, and assessment of risk predictors before conception.³⁵⁸

Women with NYHA class III or IV HF should be advised against pregnancy. Counseling regarding family planning and contraceptive options should be individualized according to

Table 6.22 – Vaccination recommendations for patients with heart failure

Recommendations	Strength of recommendation	Certainty of evidence
We recommend IN FAVOR OF annual influenza vaccination, preferably with the high-dose vaccine, to prevent mortality and worsening heart failure.	STRONG	MODERATE
We recommend IN FAVOR OF a single dose of the respiratory syncytial virus vaccine, beginning at 60 years of age, to prevent factors associated with worsening heart failure.	STRONG	MODERATE
We recommend IN FAVOR OF COVID-19 vaccination every 6 months, using the most up-to-date vaccine formulation available, to prevent factors associated with worsening heart failure.	STRONG	HIGH
We recommend IN FAVOR OF pneumococcal vaccination to prevent factors associated with worsening heart failure.	STRONG	HIGH

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the underlying etiology of cardiomyopathy, functional class, and patient biotype.³⁵⁹

For women planning pregnancy, optimization of medical therapy before conception is recommended, considering that cornerstone HF medications (ACEIs, ARBs, ARNIs, MRAs, and ivabradine) are contraindicated during pregnancy and should be replaced. Patients should also be counseled regarding the potential short- and long-term impact of pregnancy on heart disease.³⁶⁰

6.3.12. Nutrition in Heart Failure

6.3.12.1. Weight Management

Dietary interventions and weight management should be individualized according to each patient's clinical characteristics, with distinct considerations for patients with HFrEF or HFpEF.

Caloric intake should be carefully monitored for weight management, particularly in patients with obesity and HFpEF.²⁸⁵ Patients with HFrEF are at greater risk of developing cardiac cachexia, and unintentional weight loss is associated with a poorer prognosis. Therefore, intentional weight loss should not be encouraged in patients with HFrEF.^{361,362} The Mediterranean diet and the Dietary Approaches to Stop Hypertension (DASH) diet are recommended for patients with HFpEF because of their favorable effects on endothelial function, BP, and metabolic control, particularly in individuals with hypertension.³⁶² Nutritional follow-up by a registered dietitian is especially important for patients with cachexia or obesity, and self-care strategies are more effective when supported by continuous multidisciplinary care.^{11,362,363}

In patients with HF, abrupt changes in body weight (> 2 kg within 3 days) should be interpreted as a sign of fluid retention, rather than an increase in fat or lean body mass, with increased risk of DHF requiring prompt medical intervention.³⁶⁴ Therefore, patients should be advised to weigh themselves daily to monitor for weight fluctuations.

6.3.12.2. Dietary Supplements in Heart Failure

6.3.12.2.1. Omega-3 Polyunsaturated Fatty Acids

Supplementation with omega-3 fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), has been investigated as an adjunctive therapy in HF. The GISSI-HF trial³⁶⁵ demonstrated that supplementation with 1 g/day of omega-3 fatty acids produced a modest but statistically significant reduction in all-cause mortality and cardiovascular hospitalizations in patients with chronic HF. However, more recent studies have failed to confirm these benefits in HF.³⁶⁶ The conflicting findings are likely attributable to differences in study populations and omega-3 fatty acid formulations. Furthermore, high-dose omega-3 fatty acid supplementation may be associated with an increased risk of AF, particularly in individuals without preexisting cardiovascular disease. Therefore, the current evidence is insufficient to support a recommendation for the use of omega-3 polyunsaturated fatty acids in patients with HF.

6.3.12.2.2. Coenzyme Q10

Coenzyme Q10 (CoQ10) has biological properties that support its potential benefit in HF. It enhances adenosine triphosphate (ATP) production and cellular energy generation by mediating electron transport in the mitochondrial respiratory chain. In addition, CoQ10 reduces oxidative stress and stabilizes calcium-dependent ion channels in the myocardium, further promoting ATP synthesis.³⁶⁷

The multicenter Q-SYMBIO trial³⁶⁸ demonstrated that 300 mg/day of CoQ10, administered in addition to standard therapy, significantly reduced all-cause mortality, cardiovascular mortality, and HF hospitalizations. CoQ10 was also shown to be safe and well tolerated, with no significant increase in adverse events. Different meta-analyses³⁶⁹⁻³⁷¹ have suggested that CoQ10 may improve LVEF in patients with HF and reduce mortality in patients with HFrEF. However, additional well-designed studies involving more diverse patient populations are needed to confirm these findings.

6.3.12.2.3. Vitamin D

Although observational studies have associated low serum 25-hydroxyvitamin D concentrations with an increased risk of cardiovascular disease,³⁷²⁻³⁷⁴ evidence from RCTs has not demonstrated that vitamin D supplementation reduces cardiovascular risk, including in patients with HF. Thus, there is no evidence to support vitamin D supplementation as a treatment for HF. Vitamin D supplementation might be considered only in individuals with documented deficiency (< 20 ng/mL). Whenever possible, adequate vitamin D levels should be maintained primarily through an appropriate diet and moderate sun exposure.³⁷⁵

6.3.12.2.4. Hormone Replacement Therapy

Testosterone

Screening for hypogonadism in men with heart failure HF is clinically relevant, as low testosterone levels have been associated with a worse prognosis.³⁷⁶⁻³⁷⁸ Observational studies indicate that androgen deficiency may contribute to symptoms such as fatigue, reduced functional capacity, and loss of skeletal muscle mass.^{379,380} Hormonal evaluation, including measurement of total and free testosterone levels, should be considered in patients with HF who present with clinical signs suggestive of hypogonadism, such as decreased libido, erectile dysfunction, and reduced muscle mass.

Testosterone replacement therapy may improve functional capacity, increase muscle mass, and alleviate HF symptoms without a significant increase in adverse cardiovascular events during short-term follow-up.³⁸¹⁻³⁸³ However, because of the heterogeneity of the available studies and their relatively small sample sizes, the overall certainty of evidence is considered moderate. Therefore, testosterone replacement therapy might be considered for men with HF and symptomatic hypogonadism after individualized clinical assessment and careful monitoring, particularly for potential adverse effects and contraindications.

Table 6.23 summarizes the recommendations for the use of testosterone in patients with HF.

Table 6.23 – Recommendations for the use of testosterone in patients with heart failure

Recommendations	Strength of recommendation	Certainty of evidence
We recommend AGAINST the use of testosterone in the absence of a clinical and laboratory diagnosis of hypogonadism.	STRONG	HIGH

Estrogens

Estrogen replacement therapy (ERT) has been extensively studied for its impact on the cardiovascular health of postmenopausal women. Although observational studies suggest that estrogen deficiency contributes to the metabolic and hemodynamic alterations associated with HFpEF,³⁸⁴ meta-analyses have yielded conflicting results and have failed to demonstrate consistent benefits of ERT in reducing cardiovascular events.^{385,386} Consequently, the certainty of evidence supporting the use of estrogens to prevent or treat HF is considered low. Therefore, ERT is not recommended as a therapeutic strategy for HF and should be reserved for the management of menopausal vasomotor symptoms after an individualized assessment of the potential risks and benefits.

6.3.13. Special Topic: Essential Requirements for the Structure and Operation of a Heart Failure Clinic

The high morbidity and mortality associated with HF, together with its high rate of recurrent hospitalizations and

clinical complexity, pose major challenges to health care systems. In this context, and with the goal of improving follow-up, the establishment of specialized HF clinics staffed by multidisciplinary teams is essential to provide comprehensive patient care, follow-up, and monitoring.³⁵⁸

Several studies and systematic reviews have demonstrated that HF clinics improve adherence to both pharmacologic and nonpharmacologic treatment, facilitate optimization of medical therapy, reduce hospitalization rates and hospital costs, and improve patients' quality of life.^{387,388}

6.3.13.1. Team Members

The core clinical team of an HF clinic consists of a physician and a nurse. The nurse leads patient and family education programs, provides continuous patient monitoring, and coordinates multiple referrals and communication among the multidisciplinary team, including physicians, dietitians, psychologists, social workers, pharmacists, exercise physiologists, dentists, and physical therapists (Figure 6.7).

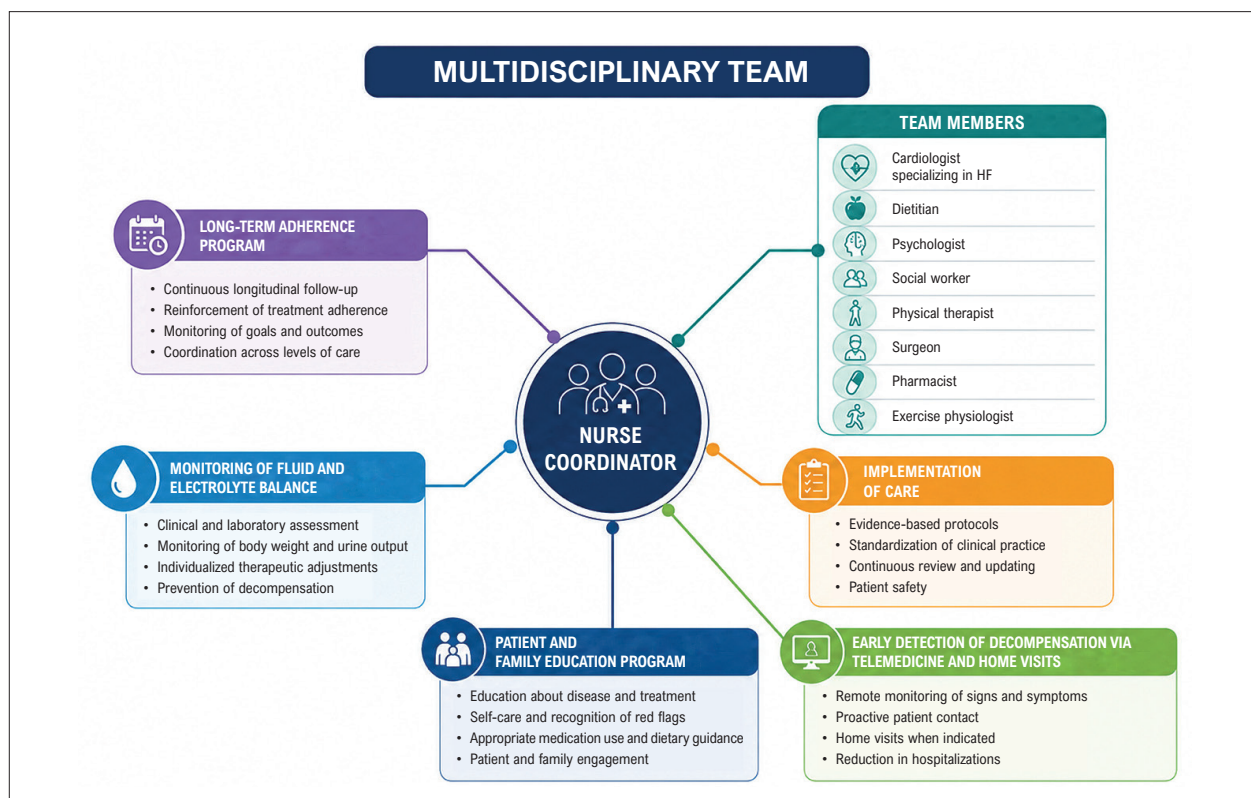


Figure 6.7 – Members of the multidisciplinary heart failure clinic team and their principal roles and responsibilities.

The nurse is responsible for educating patients, reinforcing treatment recommendations, and monitoring adherence to both pharmacologic and nonpharmacologic therapies. This includes reviewing prescribed medications and dosages, as well as providing guidance on fluid restriction (according to the patient's clinical status) and sodium restriction.³⁸⁹⁻³⁹² The nurse also plays a key role in patient follow-up through telephone contacts, particularly for high-risk patients with frequent hospitalizations, adjustment of diuretic therapy, and active outreach to patients who miss scheduled appointments.^{393,394}

7. Decompensated Heart Failure

7.1. Definitions and Fundamental Pathophysiological Aspects

Decompensated heart failure (DHF) is defined as the rapid onset of signs and symptoms in new-onset HF or the abrupt worsening of signs and symptoms of chronic HF, severe enough to prompt the patient to seek urgent medical attention, resulting in hospital admission or an emergency department visit.³⁵²

Although DHF may result primarily from an acute myocardial insult, such as fulminant myocarditis or acute myocardial infarction, most cases represent decompensation of chronic HF. In this setting, the pathophysiology of DHF is characterized by marked exacerbation of chronic neurohormonal activation, primarily involving the RAAS and the sympathetic nervous system, which lead to peripheral vasoconstriction, increasing LV afterload, reducing myocardial contractility, and accelerating structural and functional myocardial deterioration. This process also exacerbates functional MR and TR, further impairing cardiac performance by increasing filling pressures and reducing tissue perfusion. In addition, pronounced sodium and fluid retention, often accompanied by renal dysfunction, leads to hypervolemia and worsening congestion, which is the central pathophysiological feature intrinsically related to DHF and is present in the vast majority of patients hospitalized for DHF.³⁵²

7.2. Epidemiology, Diagnosis, and Prognosis

DHF is one of the leading causes of hospitalization and mortality, particularly among patients aged ≥ 65 years, and represents one of the most costly conditions for health care systems.^{4,395,396} Its incidence continues to increase because of population aging and the growing prevalence of cardiovascular risk factors. Most cases of DHF occur in patients with chronic HF who experience decompensation triggered by factors such as infection, arrhythmias, acute coronary syndrome, hypertension, myocarditis, or poor adherence to treatment. In Brazil, treatment non-adherence is a major challenge, accounting for 25% of cases of DHF and contributing to increases in rehospitalization and mortality.^{397,398}

The diagnosis of DHF is based on clinical assessment, laboratory testing, and imaging. In patients with established chronic HF, decompensation can be determined through clinical assessment alone. Additional diagnostic workup includes laboratory testing, ECG, chest radiography, and, whenever feasible, echocardiography. Among laboratory

tests, low NP levels allow for the exclusion of DHF, regardless of other diagnostic findings. In this setting, NT-proBNP levels < 300 pg/mL or BNP levels < 100 pg/mL rule out the diagnosis of DHF (Figure 7.1).³⁹⁹⁻⁴⁰¹ Additional diagnostic modalities, such as the detection of pulmonary B-lines on lung ultrasound (LUS) to assess extravascular lung water, are increasingly used in clinical practice to indicate the presence of HF in patients with dyspnea.¹⁰¹ Other laboratory findings are important for determining the patient's hemodynamic profile (renal function, liver function, and arterial blood gases) and for identifying the cause of decompensation, such as complete blood count, inflammatory markers, troponin, D-dimer, blood glucose, and thyroid profile (Chart 7.1).

Hospitalization for DHF is a marker of poor prognosis. In-hospital mortality is high, ranging from 4% to 10%.¹⁰¹ One-year mortality after discharge reaches 25% to 30%.^{402,403} In Brazil, recent data from the BREATHE registry showed a cumulative 12-month mortality of 27.7%, with readmission rates of 24.3% at 90 days and 44.4% at 12 months.^{404,405} Predictors of an adverse prognosis include advanced age, comorbidities (diabetes, CKD, and anemia), hypotension, and hypoperfusion at presentation.^{23,406}

7.3. Clinical Presentations

The four main clinical presentations of DHF, which may overlap, are acutely decompensated chronic HF (approximately 60% of cases), new-onset HF/acute pulmonary edema (30%), isolated right ventricular (RV) dysfunction (3.5–5%), and cardiogenic shock (CS; 3–5%).^{1,4,11,404,406-414}

Clinical presentations differ in the degree of pulmonary or systemic congestion and the presence or absence of tissue hypoperfusion.^{11,404,408}

7.3.1. Decompensated Chronic Heart Failure and De Novo Acute Heart Failure

DHF may develop either progressively or abruptly in patients with preexisting chronic HF—decompensated chronic HF. Alternatively, signs and symptoms of DHF may occur in patients with no prior history of HF or structural heart disease—new-onset DHF.

Distinguishing between these 2 clinical presentations improves understanding of the pathophysiology of decompensation and facilitates selection of the most appropriate therapeutic strategy, which should be initiated immediately upon hospital admission.^{1,411-413}

Decompensated chronic HF is the most common presentation, accounting for approximately 50% to 70% of cases.⁴⁰⁷ Symptoms typically develop gradually. These patients usually have significant systolic dysfunction with progressive sodium and fluid retention. Systemic congestion predominates, resulting in a predominantly cardiac (congestive) profile, which is less frequently accompanied by tissue hypoperfusion. The most common complaints are dyspnea, peripheral edema (especially in the lower extremities), and weight gain. The treatment plan for decompensated chronic HF should prioritize early decongestion to achieve rapid and effective symptom relief.^{1,404-408}

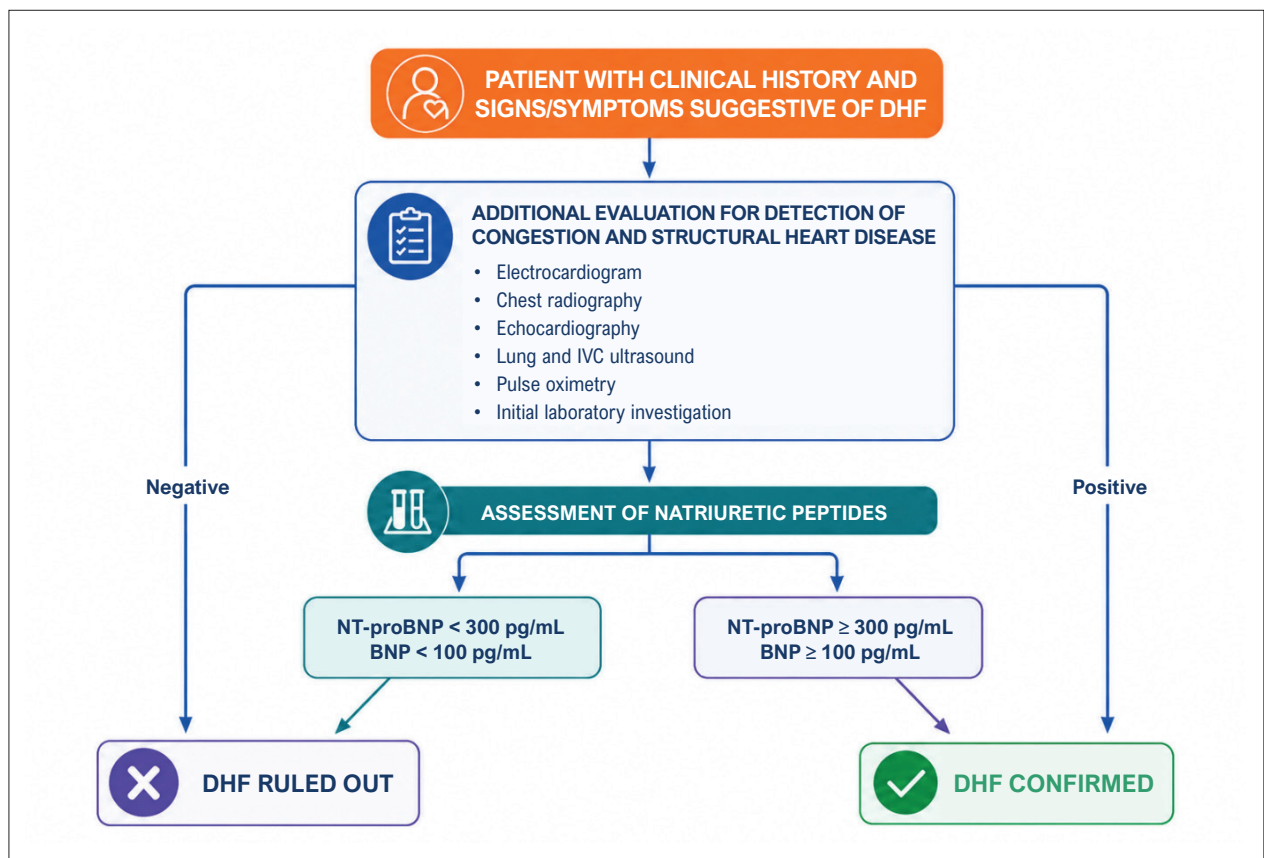


Figure 7.1 – Diagnostic algorithm for decompensated heart failure. BNP: B-type natriuretic peptide; HF: heart failure; DHF: decompensated heart failure; NT-proBNP: N-terminal pro-B-type natriuretic peptide; IVC: inferior vena cava.

Chart 7.1 – Most relevant laboratory tests in decompensated heart failure

Test	Time of assessment	Potential findings	Diagnostic value in DHF
ECG	Admission, during hospitalization, pre-discharge	Arrhythmias, myocardial ischemia	Exclusion of ACS, arrhythmias
Chest radiography	Admission, during hospitalization	Congestion, pulmonary infection, pleural effusion	Confirmation of DHF
Lung US	Admission, during hospitalization, pre-discharge	Congestion	Confirmation of DHF
Echocardiography	Admission, during hospitalization, pre-discharge	Congestion, cardiac dysfunction, mechanical causes	High predictive value
Natriuretic peptides	Admission, pre-discharge	Congestion	High negative predictive value for DHF
Troponin	Admission	Myocardial injury	Exclusion of ACS
Creatinine	Admission, during hospitalization, pre-discharge	Renal dysfunction	Prognostic assessment and treatment
Sodium/potassium	Admission, during hospitalization, pre-discharge	Electrolyte disturbances	Prognostic assessment and treatment
Iron studies (ferritin, serum iron, TSAT)	Pre-discharge	Iron deficiency	Prognostic assessment and treatment

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TSH	Admission	Hypothyroidism/ hyperthyroidism	Confirmation of thyroid disease
<i>D-dimer</i>	Admission	Pulmonary embolism	Useful for excluding pulmonary embolism
Procalcitonin	Admission	Pneumonia	Useful for diagnosing pneumonia
Serum lactate	Admission, during hospitalization	Lactic acidosis	Useful for diagnosing hypoperfusion
Pulse oximetry and blood gas analysis	Admission, during hospitalization	Respiratory failure	Useful for assessing respiratory function

ECG: electrocardiogram; HF: heart failure; DHF: decompensated heart failure ; TSAT: transferrin saturation; TSH: thyroid-stimulating hormone; US: ultrasound.

New-onset DHF accounts for approximately 40% of presentations. Symptoms generally evolve more rapidly, often within hours. Its pathophysiology is closely related to an abrupt increase in afterload leading to worsening diastolic dysfunction or to acute impairment of ventricular contractility. The most common clinical manifestation is dyspnea with hypoxemia resulting from severe pulmonary congestion (pulmonary edema). Peripheral edema and weight gain are uncommon, characterizing a predominantly “vascular” profile, in which management should prioritize the use of vasodilators^{1,407} (Chart 7.2).

Table 7.1 summarizes the recommendations for the use of clinical presentation profiles.

Approximately 50% of patients have an identifiable precipitating factor responsible for DHF. Recognition and

appropriate management of these triggers are essential for achieving clinical stabilization and reducing the risk of recurrent decompensation after hospital discharge^{407,410,414} (Chart 7.3).

Table 7.2 summarizes the recommendations for the identification of precipitating factors in DHF.

7.4. Treatment Strategies

7.4.1. Initial Approach: Risk Assessment and the Need for Immediate Specific Therapies

The initial evaluation of patients presenting to the emergency department with suspected DHF should follow a systematic 3-step approach:

Chart 7.2 – Clinical and Pathophysiological Characteristics of Decompensated Chronic Heart Failure and Decompensated Heart Failure¹

	Decompensated chronic HF (cardiac/ congestive profile)	New-Onset DHF (Vascular Profile)
Mechanism	Impaired contractility/sodium and water retention	Increased afterload with worsening diastolic dysfunction, or acute impairment of myocardial contractility
Congestion pattern	Global increase in blood volume	Redistribution of blood volume, with pulmonary congestion but without systemic/peripheral hypervolemia
Symptom onset	Gradual (days)	Rapid (hours)
Peripheral edema	Frequent	Seldom
Weight gain	Frequent	Seldom
Systolic function	Reduced	Normal or reduced
Hypoxemia	Possible	Very frequent
Blood pressure	Normal or low	Normal or high
Treatment	Diuretics (decongestion) Assess hypoperfusion and the need for a combination of inotropic agents/vasopressors/mechanical circulatory support	Vasodilators Judicious use of diuretics

HF: heart failure.

Table 7.1 – Recommendations for the use of clinical presentation profiles

Recommendation	Strength of recommendation	Certainty of evidence
We recommend classifying DHF by clinical presentation—decompensated chronic HF versus new-onset DHF—and recognizing their distinct pathophysiological features to guide appropriate treatment.	STRONG	MODERATE

1. Identify and promptly correct life-threatening conditions (CS and/or respiratory failure).
2. Establish the diagnosis of DHF and identify etiologies requiring disease-specific treatment.
3. Determine the initial therapeutic strategy based on the patient's noninvasive clinical/hemodynamic profile and patient disposition (Figure 7.2).

Ideally, these 3 steps should be completed within the first 60 minutes of presentation to enable prompt initiation of treatment for DHF and improve in-hospital outcomes.^{4,410,415} During the initial emergency assessment of patients with suspected DHF, clinicians should first identify conditions associated with an immediate threat to life, such as CS and respiratory failure, for the prompt initiation of appropriate interventions, including ventilatory

Chart 7.3 – Major precipitating factors in decompensated heart failure^{410,414}

Suboptimal medical therapy
Non-adherence to prescribed medications
Excessive fluid and/or sodium intake
Infections
Use of contraindicated medications (eg, nonsteroidal anti-inflammatory drugs)
Exacerbation of hypertension
Pulmonary embolism
Myocardial ischemia
Tachyarrhythmias or bradyarrhythmias
Alcohol or illicit drug abuse
Renal failure
Acute worsening of mitral or aortic regurgitation
Pericardial tamponade
Acute coronary syndrome
Thyroid disease
Anemia
Endocarditis

Table 7.2 – Recommendations for the identification of precipitating factors in decompensated heart failure

Recommendation	Strength of recommendation	Certainty of evidence
We recommend IN FAVOR OF early identification and correction of potential precipitating factors of decompensated heart failure to achieve more rapid clinical stabilization, reduce mortality, and lower rehospitalization rates.	STRONG	HIGH

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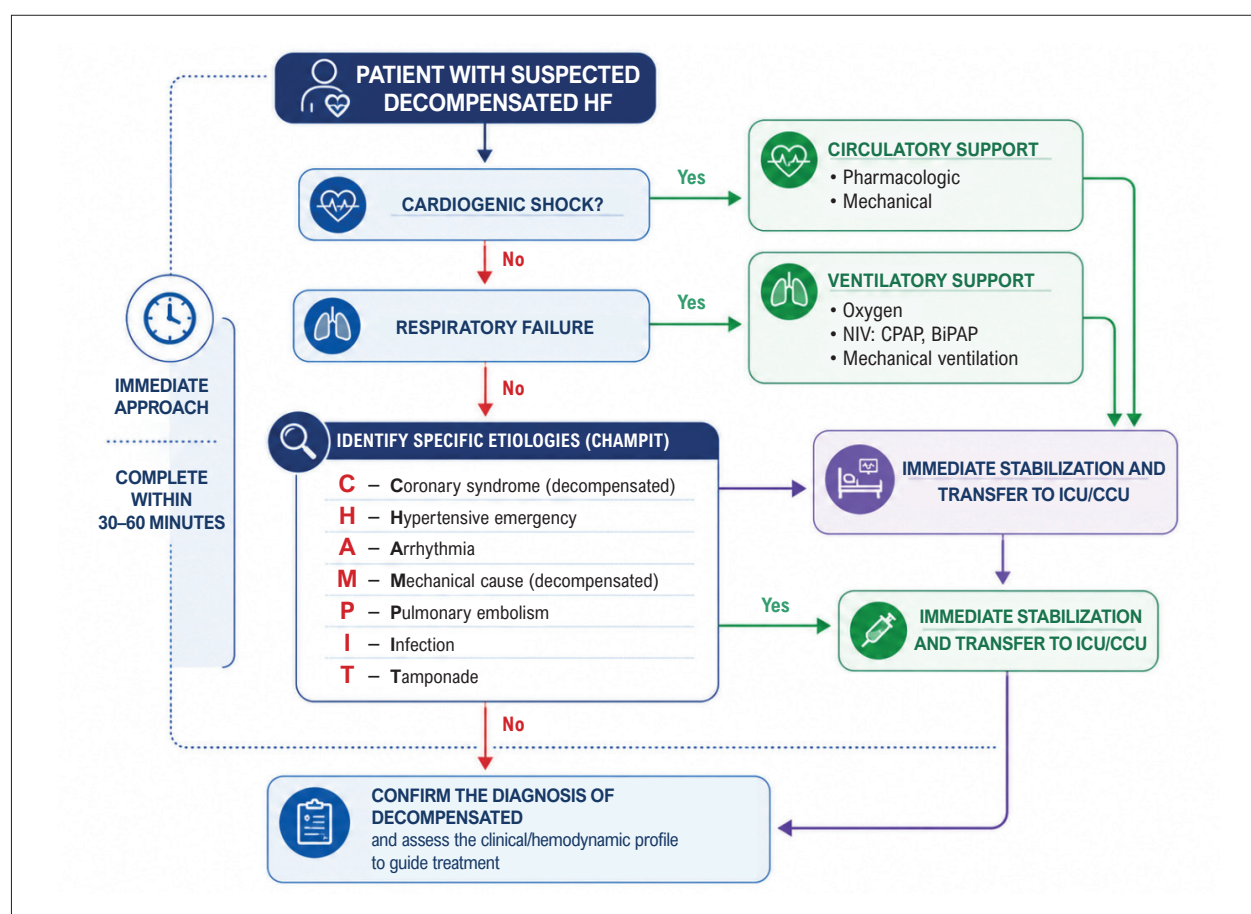


Figure 7.2 – Initial steps in the approach to patients with decompensated heart failure. BiPAP: bilevel positive airway pressure; CPAP: continuous positive airway pressure; ICU: intensive care unit; HF: heart failure; DHF: decompensated heart failure; CCU: coronary care unit; NIV: noninvasive ventilation.

support and pharmacologic and/or mechanical circulatory support (MCS).

This should be followed by a rapid investigation for specific etiologies of DHF that require targeted therapy, including arrhythmias, acute ischemic ECG changes, elevated troponin levels, infection, and signs of pericardial tamponade (Figure 7.3). These conditions should be identified and treated with targeted therapies within the first 60 minutes of admission, because early disease-specific intervention is a major determinant of in-hospital outcomes.^{1,404,416}

Once the diagnosis of DHF has been established, the initial treatment strategy and patient disposition should be guided by the noninvasive clinical/hemodynamic profile (Figure 7.3), the pattern of decompensation (vascular vs. congestive), and the level of systemic BP.

Patients with hemodynamic instability or respiratory failure should be managed in an intensive care unit.

7.4.2 Initial Treatment Based on the Noninvasive Clinical/Hemodynamic Profile

The primary goals of the initial management of DHF are to prevent death and achieve rapid symptomatic improvement

by relieving congestion and/or correcting low cardiac output. The initial therapeutic targets are as follows: (1) relief of dyspnea; (2) urine output ≥ 1.5 mL/kg/h during the first 6 hours; and (3) hemodynamic stability.

Patients with hypoxemia ($\text{SpO}_2 < 90\%$) should receive supplemental oxygen. Noninvasive positive-pressure ventilation (NIPPV) should be initiated early whenever indicated in patients with significant dyspnea (respiratory rate > 25 breaths/min and $\text{SpO}_2 < 90\%$). A meta-analysis suggests that this strategy may not only improve dyspnea and reduce the need for intubation but also reduce mortality compared with conventional oxygen therapy.⁴¹⁷

Each clinical/hemodynamic profile requires a distinct pharmacologic approach. Figure 7.4 provides the therapeutic algorithm for DHF in patients classified as “warm and dry” (profile A), who exhibit neither congestion/hypervolemia nor signs of hypoperfusion/low cardiac output, the primary objective is to ensure that they are receiving optimal GDMT, while adjusting the doses and reassessing, through appropriate diagnostic methods, whether dyspnea may have an alternative cause, as these patients appear to be clinically compensated.

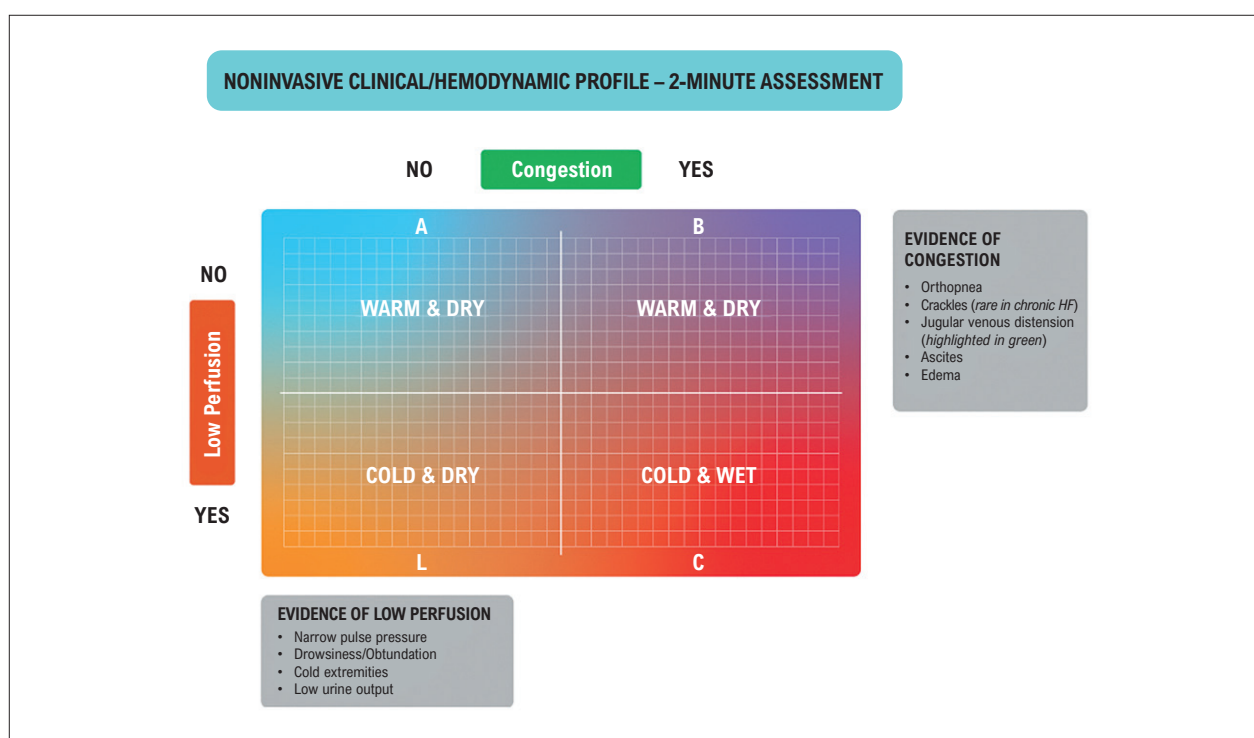


Figure 7.3 – Characterization of the 4 noninvasive clinical/hemodynamic profiles of decompensated heart failure. Source: Stevenson LW. *Eur J Heart Fail.* 1999; 1:251.

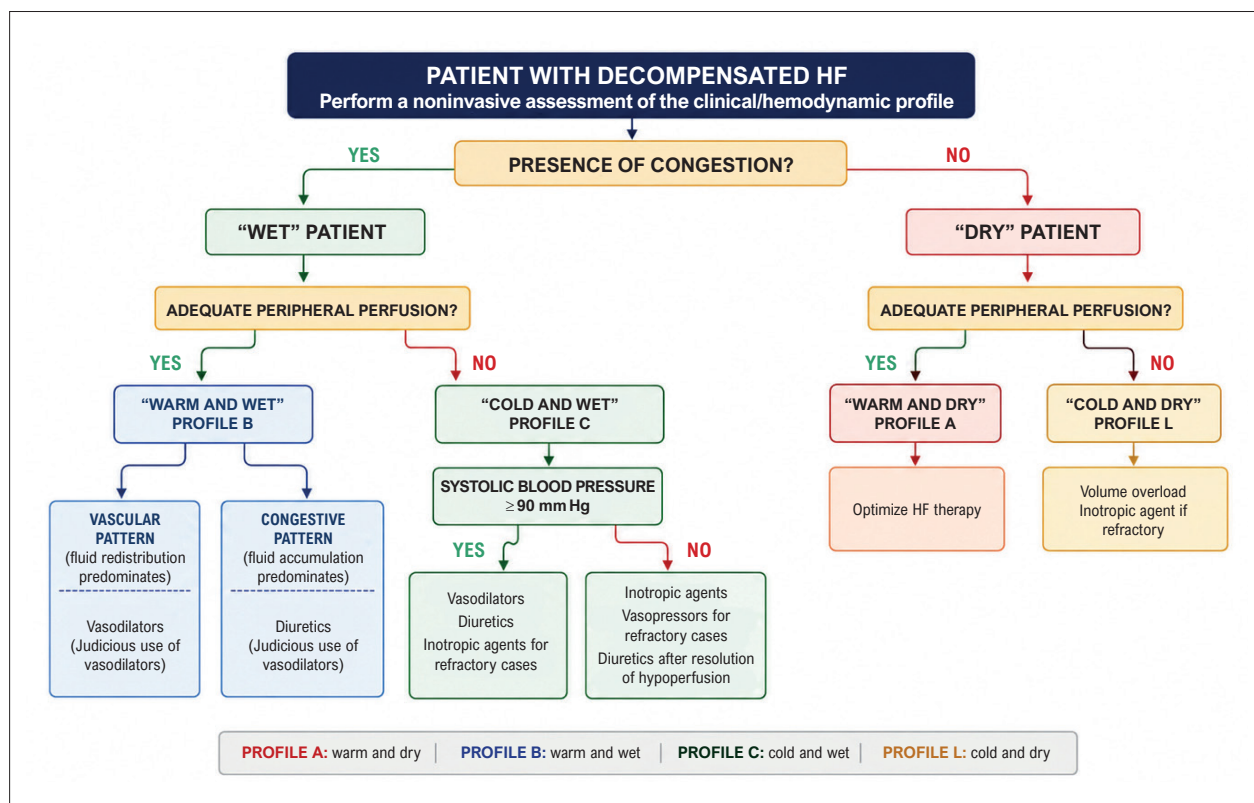


Figure 7.4 – Initial treatment algorithm for decompensated heart failure according to noninvasive clinical/hemodynamic profiles, pattern of decompensation (vascular vs. congestive), and the level of systemic blood pressure. HF: heart failure.

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Patients classified as “warm and wet” (profile B), who exhibit congestion/hypervolemia without signs of hypoperfusion or low cardiac output, should initially be treated with intravenous vasodilators and diuretics (see the section on decongestive therapy below), followed by transition to oral therapy after clinical improvement. Intravenous loop diuretics are the first-line treatment.

Intravenous vasodilators, most commonly nitroglycerin, are frequently used because of their ease of administration and favorable safety profile, providing more rapid relief of dyspnea. Sodium nitroprusside is an alternative, particularly in patients with an inadequate initial response, severe hypertension, or marked pulmonary hypertension.

Vasodilator therapy should be progressively titrated until the desired clinical response is achieved or the maximum tolerated dose is reached. Treatment tolerance is determined by the absence of signs or symptoms of hypoperfusion while maintaining SBP $\geq$ 90 mm Hg. After the first 24–48 hours, if the expected response has been achieved, the same therapeutic strategy should be maintained while oral vasodilators are introduced to allow gradual withdrawal of intravenous agents.

Patients classified as “cold and wet” (profile C), who exhibit congestion/hypervolemia with signs of hypoperfusion or low cardiac output, should receive intravenous diuretics (using dosing and response assessment similar to those for profile B) combined with pharmacologic measures to increase cardiac output. In patients with SBP $\geq$ 90 mm Hg, intravenous sodium nitroprusside may be used. Inotropic therapy is recommended only for patients with SBP < 90 mm Hg or for those who fail to respond adequately to vasodilator and diuretic therapy. Dobutamine is generally the preferred first-line inotropic agent. However, once BP has improved sufficiently following initiation of inotropic therapy, intravenous vasodilator therapy should be started

whenever possible to facilitate early discontinuation of the inotropic agent.^{418–421}

If clinical and laboratory markers of tissue perfusion (serum lactate concentration) fail to improve after initiation and dose optimization of the initial inotropic agent, and BP remains insufficient (SBP < 90 mm Hg) to permit vasodilator therapy, the addition of a second inotropic agent (milrinone or levosimendan) should be considered.

An intermediate profile, referred to as the “lukewarm profile,” may also be recognized during treatment monitoring. These patients initially present as profile B but respond poorly to intravenous diuretic therapy, with persistent congestion and WRF despite the absence of signs of hypoperfusion or low cardiac output. In this setting, WRF is considered a marker of renal hypoperfusion, reflecting occult low cardiac output that is not apparent on clinical examination. Management should therefore focus on increasing cardiac output using sodium nitroprusside or inotropic agents (see the section 7.14.2.^{409,415}

Finally, patients with a “cold and dry” (profile L), who do not exhibit congestion/hypervolemia but do exhibit signs of hypoperfusion or low cardiac output, should initially receive fluid resuscitation.¹¹ Rapid intravenous boluses of 250 mL of isotonic saline (0.9% saline solution) should be administered, followed by clinical and hemodynamic reassessment after each bolus. If no improvement is observed within the first 2 hours of adequate fluid resuscitation, insertion of a central venous catheter to allow continuous monitoring of central venous pressure (CVP) and central venous oxygen saturation (ScvO₂), or placement of a Swan–Ganz catheter,^{422,423} together with invasive arterial pressure monitoring, is recommended to guide further therapeutic adjustments.

Table 7.3 summarizes the recommendations for the initial management of DHF according to the noninvasive clinical/hemodynamic profiles.

Table 7.3 – Recommendations for the initial management of decompensated heart failure

Recommendation	Strength of recommendation	Certainty of evidence
In patients with signs and symptoms of hypervolemia, we recommend IN FAVOR OF early initiation of intravenous diuretic therapy (furosemide) within 1 hour of presentation, with subsequent dose adjustment, to achieve an adequate diuretic response and effective decongestion for symptom relief.	STRONG	MODERATE
In selected patients classified as profile B (“warm and wet”), we recommend IN FAVOR OF the use of intravenous vasodilators to achieve more rapid symptom relief.	WEAK	LOW
In patients classified as profile C (“cold and wet”) with systolic blood pressure > 90 mm Hg, we recommend IN FAVOR OF the use of an intravenous vasodilator (sodium nitroprusside) to improve cardiac output and tissue perfusion.	WEAK	LOW
In patients classified as profile C (“cold and wet”) with systolic blood pressure < 90 mm Hg, we recommend IN FAVOR OF the use of an inotropic agent (dobutamine) to improve cardiac output and tissue perfusion.	STRONG	LOW
In patients classified as profile L (“cold and dry”), we recommend IN FAVOR OF fluid resuscitation with saline solution until perfusion/volume is adequate.	STRONG	LOW

7.4.3. Oral Medications at Hospital Admission

Upon admission for DHF, patients who are already receiving GDMT and present with stable hemodynamics, observational studies have shown that continuation of these medications is safe and well tolerated, provided there are no contraindications such as severe renal dysfunction or hyperkalemia. Conversely, discontinuation of FMT during hospitalization for DHF has been associated with increased mortality and should therefore be avoided.^{424,425}

In patients who were not previously receiving DHF, initiation of this therapy can be performed safely after clinical stabilization rather than at the time of hospital admission. Appropriate candidates include patients who no longer require intravenous vasodilator or inotropic support and who are receiving a stable dose of intravenous diuretics or have already achieved euvoolemia.¹⁴³

7.5. Decongestive Therapy

7.5.1. Loop Diuretics

Loop diuretics, particularly furosemide, are the cornerstone of treatment for DHF with volume overload. The principal RCT evaluating their use in this setting was the DOSE-HF trial,⁴²⁶⁻⁴²⁸ which compared different intravenous furosemide administration strategies. The results demonstrated improvement in the clinical signs of congestion with higher doses – defined as 2.5 times the patient's previous oral dose – but no clear benefit of routine continuous infusion over intermittent bolus administration.

Loop diuretics exhibit a threshold effect, below which there is no meaningful diuretic response. Once this threshold is exceeded, the response tends to be dose-dependent, with proportional increases in natriuresis and diuresis. The threshold dose of furosemide varies according to the patient's clinical condition, including factors such as renal function and volume status. In clinical practice, when the response to decongestive therapy is suboptimal, increasing the diuretic dose is generally more effective than repeating the same dose at shorter intervals. This is because when the concentration of the drug in the renal tubules does not reach the required threshold, multiple administrations of subtherapeutic doses tend to be ineffective. Moreover, this approach may promote the activation of compensatory sodium-retaining mechanisms, such as the RAAS. Continuous furosemide infusion remains a feasible alternative in patients who are refractory to intermittent bolus administration, as it avoids abrupt fluctuations in intravascular volume and attenuates peak serum drug concentrations, potentially reducing toxicity while providing more sustained diuresis.

Combining diuretics with different mechanisms of action may produce sequential nephron blockade, thus enhancing the diuretic effect by reducing sodium reabsorption in the proximal tubule (acetazolamide) or by attenuating the effects of hypertrophy and sodium reabsorption in the distal tubule (hydrochlorothiazide).

Therefore, in DHF with hypervolemia, furosemide should be administered using a dose-escalation strategy, as summarized in Figure 7.5. In patients not previously treated with furosemide, the initial dose should be 20–40 mg as an intravenous bolus, followed by assessment of the diuretic response over the subsequent 6 hours. In patients already receiving oral furosemide, treatment should be initiated with an intravenous bolus equivalent to 1–2 times the total daily oral dose.

Prospective observational studies and registry data have shown that earlier initiation of intravenous furosemide after patient presentation (≤ 6 hours) is associated with lower in-hospital mortality. Therefore, the first dose of intravenous furosemide should ideally be administered within 1 hour of confirmation of the diagnosis DHF with hypervolemia.

If an adequate diuretic response is achieved in the first 6 hours after the initial intravenous bolus (urine output > 100 – 150 mL/hour), the same bolus dose may be repeated every 12 hours. If the response is inadequate, the furosemide dose should be doubled, followed by another 6-hour period of observation. This dose-escalation strategy should be repeated until an adequate response is achieved or the maximum recommended daily dose of 400–600 mg is reached. In patients not achieving an effective diuretic response despite the maximum furosemide dose, another diuretic acting at a different nephron site, such as a thiazide diuretic or acetazolamide, may be added. The most commonly used agent is hydrochlorothiazide, administered orally at 50–100 mg once daily. Continuous intravenous furosemide infusion may also be considered. Although the usual maximum furosemide daily dose is 400–600 mg, doses of up to 1000 mg/day might be considered in patients with severely impaired renal function.

Recently, the PUSH-AHF trial evaluated natriuresis-guided diuretic therapy *versus* standard of care. In the natriuresis-guided arm, spot urinary sodium was measured at 2, 6, 12, 18, 24, and 36 hours after initiation of intravenous loop diuretics. Diuretic therapy was intensified using a stepwise approach when the response was considered insufficient (spot urinary sodium < 70 mmol/L and/or urine output < 150 mL/hour). This strategy resulted in significantly improved diuresis and natriuresis at 24 and 48 hours without WRF or electrolyte disturbances, although it did not reduce mortality or rehospitalization at 180 days.⁴¹⁸ Intravenous diuretic therapy should be continued during hospitalization as long as hypervolemia persists (Figure 7.6). The degree of decongestion should be monitored throughout the hospital stay (see the section on monitoring decongestion below). An adequate response to diuretic therapy during hospitalization is defined as a urine output > 3 – 4 L/24 hours, combined with fluid restriction to 2 L/24 hours. Patients not achieving these targets should have the furosemide dose increased (typically by doubling the dose), whereas those with an excessive response may require dose reduction (Figure 7.6). Diuretic therapy should be maintained until complete decongestion is achieved, after which the patient should undergo evaluation and preparation for hospital discharge (see the dedicated section below).

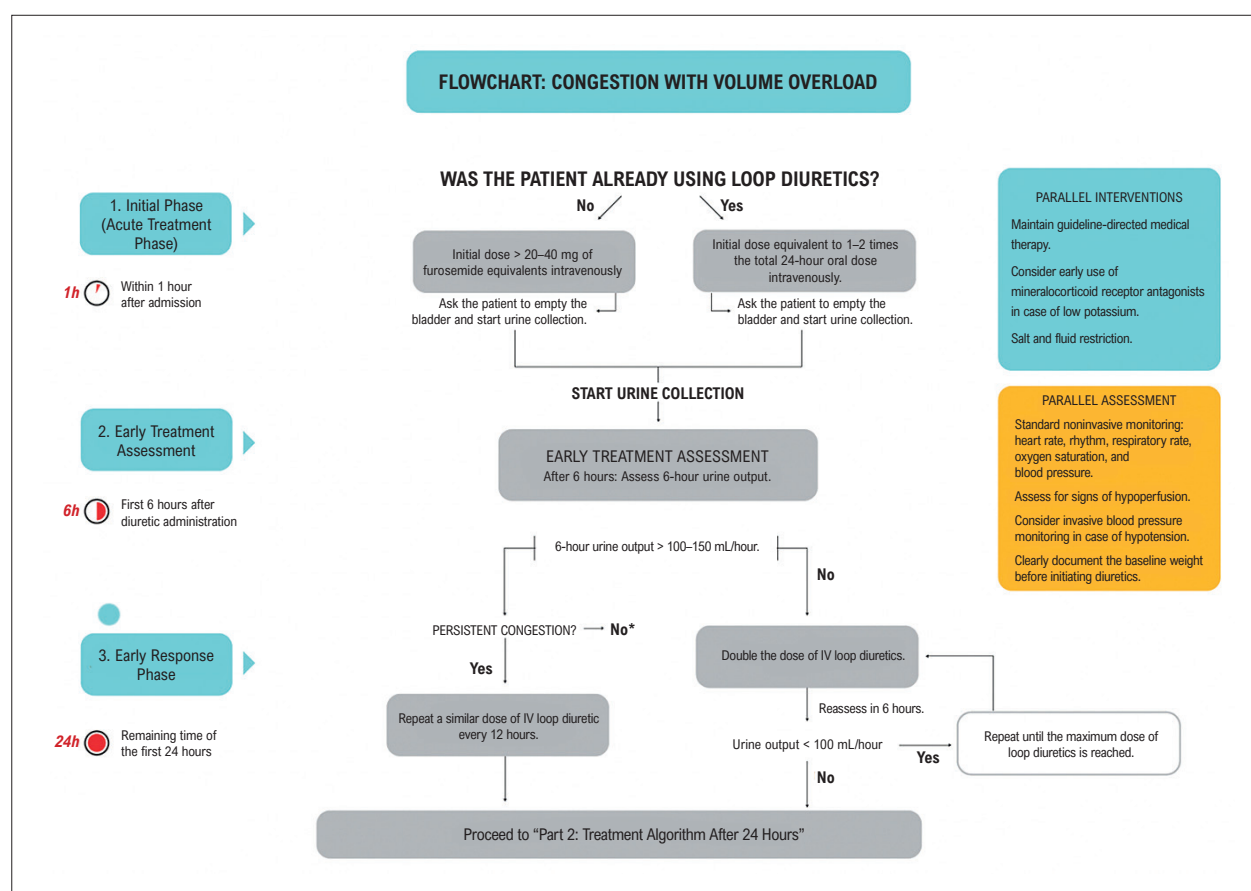


Figure 7.5 – Initial loop diuretic dosing, assessment of diuretic response, and dose adjustment strategy in the treatment of decompensated heart failure. HF: heart failure; IV: intravenous. *Consider early use of mineralocorticoid receptor antagonists in case of low potassium.

7.5.2. Preemptive Sequential Nephron Blockade at Hospital Admission

Some recent studies have evaluated the preemptive use of diuretics for sequential nephron blockade at hospital admission in patients with DHF and hypervolemia. The rationale for this approach is to achieve more rapid decongestion, while maintaining safety, and to reduce hospital length of stay.

The CLOROTIC trial⁴²⁹ enrolled 230 patients with DHF who were randomly assigned to receive oral hydrochlorothiazide (25–100 mg/day, adjusted according to eGFR) or placebo, both in combination with intravenous furosemide. The trial had 2 coprimary endpoints: changes in body weight and changes in patient-reported dyspnea from baseline to 72 hours of randomization. Patients treated with hydrochlorothiazide experienced greater weight loss at 72 hours than those receiving placebo (–2.3 vs. –1.5 kg; adjusted estimated difference, –1.14 kg; 95% CI, –1.84 to –0.42 kg; $p = 0.002$). However, changes in patient-reported dyspnea were similar in both groups. Increases in serum creatinine levels were more frequent in the hydrochlorothiazide group than in the placebo group (46.5% vs. 17.2%; $p < 0.001$). Rates of HF rehospitalization, all-cause mortality, and hospital length of stay were comparable between groups.

The ADVOR trial⁴³⁰ was a multicenter, double-blind, randomized, placebo-controlled trial that enrolled 519 patients with DHF, clinical signs of volume overload (eg, edema), and elevated NT-proBNP or BNP levels. Participants were randomly assigned to receive intravenous acetazolamide (500 mg once daily) or placebo, both in addition to standardized intravenous loop diuretic therapy. The primary endpoint, successful decongestion (defined as the absence of signs of volume overload within 72 hours of randomization and without an indication for escalation of decongestive therapy), was achieved in 42.2% of patients receiving acetazolamide (108 of 256) and 30.5% of those receiving placebo (79 of 259), with a risk ratio of 1.46 (95% CI, 1.17–1.82; $p < 0.001$). Rehospitalization for HF or death from any cause occurred in 29.7% of patients in the acetazolamide group (76 of 256) and 27.8% of those in the placebo group (72 of 259), with a risk ratio of 1.07 (95% CI, 0.78–1.48). Mean hospital length of stay was 1 day shorter in the acetazolamide group than in the placebo group (8.8 vs. 9.9 days). No significant differences in adverse events were observed between the groups.

Because intravenous acetazolamide is unavailable in many countries, including Brazil, the recent ORION-A trial evaluated the addition of oral acetazolamide to standard

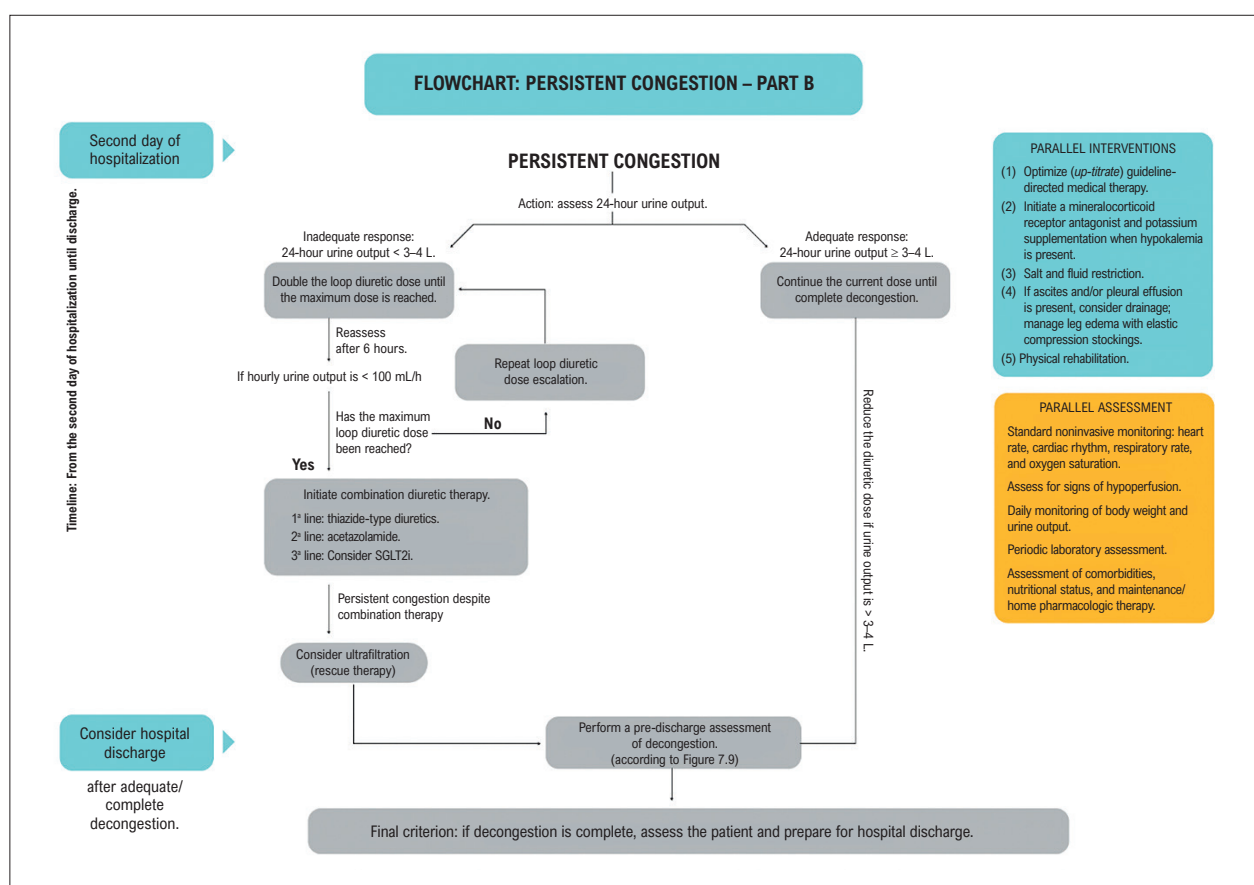


Figure 7.6 – Adjustment of loop diuretic dosage during hospitalization according to treatment response and the presence of persistent congestion.

therapy in 416 patients hospitalized for decompensated chronic HF and demonstrated that this strategy significantly increased urine output during the first 72 hours and natriuresis on day 2 compared with standard therapy alone. In addition, oral acetazolamide was safe and not associated with serious adverse events.⁴³¹

A recent meta-analysis⁴³² using the GRADE approach to assess the certainty of evidence included 4 RCTs, 3 of which evaluated oral acetazolamide. A total of 634 patients with DHF were included, with a mean age ranging from 68 to 81 years and follow-up periods ranging from 3 days to 34 months. Compared with standard therapy alone, the addition of acetazolamide at hospital admission significantly increased urine output (mean difference, 899.2 mL; 95% CI, 249.5–1549.0; $p < 0.01$) and natriuresis (mean difference, 72.44 mmol/L; 95% CI, 39.4–105.4; $p < 0.01$) within 48 hours of administration. No association was observed between acetazolamide use and WRF (RR, 2.4; 95% CI, 0.4–14.2; $p = 0.3$) or all-cause mortality (RR, 1.2; 95% CI, 0.8–1.9; $p = 0.3$). Clinical decongestion was significantly higher in the acetazolamide group (RR, 1.35; 95% CI, 1.09–1.68; $p = 0.01$).

Therefore, the available evidence suggests that oral acetazolamide, at doses of 250–500 mg/day, is an effective

adjunct to standard therapy in patients with DHF, promoting greater diuresis, natriuresis, and clinical decongestion while reducing hospital length of stay. This strategy appears to be safe with respect to WRF but has not been associated with a reduction in mortality.

Table 7.4 summarizes the recommendations for the preemptive use of acetazolamide in the treatment of DHF.

7.5.3. Management of Refractory Congestion

Approximately 80% of patients hospitalized with HF present with hypervolemia, making congestion – rather than hypoperfusion – the principal pathophysiological mechanism underlying decompensation, as demonstrated in registries such as the BREATHE registry⁴³³ and the BREATHE Extension.²³ Several factors may contribute to volume overload, including inadequate diuretic dosing, excessive sodium and fluid intake, impaired intestinal drug absorption, and resistance to diuretic therapy.

In this setting, diuretic therapy remains the cornerstone of treatment for patients with DHF and clinical signs of volume overload. Escalating doses of intravenous loop diuretics are recommended, as discussed in Section 7.5.1. However, in more severe presentations of DHF, particularly in the presence

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Table 7.4 – Recommendations for the preemptive use of combination diuretic therapy at hospital admission in patients with decompensated heart failure

Recommendation	Strength of recommendation	Certainty of evidence
In patients presenting with hypervolemia, we recommend IN FAVOR OF adding oral acetazolamide to standard intravenous furosemide therapy at hospital admission to achieve more rapid and complete decongestion and reduce hospital length of stay.	STRONG	MODERATE

of concomitant renal dysfunction, the efficacy of loop diuretics may be impaired, resulting in refractory congestion and limiting therapeutic options.⁴³⁴ In these cases, adjunctive strategies, including the addition of diuretics with different mechanisms of action or, when appropriate, renal replacement therapy, may be required to achieve adequate decongestion (Figure 7.7 and Table 7.5).^{435,436}

7.5.4. Renal Replacement Therapy

In the most severe cases of DHF, concomitant renal dysfunction and diuretic resistance may substantially limit the therapeutic options available to relieve volume overload. Extracorporeal ultrafiltration (UF) removes plasma water from whole blood as it passes through an extracorporeal hemofilter, in response to a transmembrane pressure gradient. Solutes freely cross the semipermeable membrane, allowing the removal of isotonic fluid without significant changes in electrolyte or other solute concentrations and without direct RAAS activation.

Modern UF systems are relatively simple to operate and allow adjustment of the fluid removal rate. UF is indicated as an adjunctive therapy in patients with DHF and volume overload refractory to diuretic therapy. However, RCTs evaluating its benefits have yielded conflicting results. The RAPID-CHF trial⁴³⁷ and the UNLOAD trial⁴³⁸ demonstrated greater fluid removal in the UF group, although both studies were criticized because relatively low doses of diuretics were used in the control groups. In contrast, the CARESS-HF trial⁴³⁹ employed a more intensive treatment strategy in the control group, with the aggressive use of diuretics, inotropic agents, and/or vasodilators, but found no significant differences between the groups. It is noteworthy that the UF rate in CARESS-HF was set at only 200 mL/hour, whereas rates of up to 500 mL/hour were used in the UNLOAD trial.

The AVOID-HF trial⁴⁴⁰ reported a higher incidence of adverse events with UF, including infections, bleeding, hypotension, and acute coronary syndrome. Conversely, the ULTRADISCO study⁴⁴¹ showed greater weight loss, improved symptoms, and significant reductions in NT-proBNP levels and SVR with UF. These conflicting results indicate that both the optimal UF rate and the patient populations most likely to benefit from this strategy remain to be clearly established.

7.5.5. Other Pharmacologic Approaches for Refractory Congestion

Therapies with dopamine, nesiritide, and vasopressin antagonists have a limited role in the management of volume overload in patients with DHF.

The combination of hypertonic saline (150 mL of 1.4%–4.6% NaCl) with high-dose furosemide has also emerged as a potential therapeutic option in cases of refractory hypervolemia. By its osmotic effect, hypertonic saline shifts fluid from the extravascular to the intravascular compartment, facilitating its elimination through the diuretic action of intravenous furosemide.^{442–444}

Table 7.5 summarizes the recommendations for the management of refractory congestion in HF.

7.6. Monitoring Decongestion

The treatment of hypervolemia/congestion is the cornerstone of DHF management, and methods to monitor decongestion should be used to assess the response to diuretic therapy and to detect residual congestion before hospital discharge. For this purpose, clinical congestion scores and point-of-care ultrasound (POCUS) may be used. POCUS may include lung ultrasound (LUS), inferior vena cava (IVC) ultrasound, and assessment using the Venous Excess Ultrasound Score (VExUS)..

7.6.1. Clinical Congestion Scores

Clinical assessment and physical examination are useful for detecting signs of congestion and can be used to monitor their resolution during diuretic therapy.^{445,446} To standardize this assessment in a semiquantitative manner, several clinical congestion scores have been developed. The most widely used in the setting of DHF is the congestion score from the EVEREST trial, which has been shown to correlate with post-discharge prognosis.⁴⁴⁷ This score is calculated by summing 6 clinical variables (dyspnea, orthopnea, fatigue, jugular venous distention, pulmonary rales, and edema), each scored from 0 to 3 according to severity (Chart 7.4). The EVEREST trial also standardized the composite congestion score (CCS), calculated by summing the individual scores for orthopnea, jugular venous distention, and edema, which are the signs/symptoms most strongly associated with the presence of hypervolemia/congestion (Chart 7.4).

In a post hoc analysis of the placebo group, including 2061 patients, the mean (SD) CCS decreased significantly from 4.07 (1.84) at hospital admission to 1.11 (1.42) at discharge, when nearly three-quarters of patients had a CCS of 0 or 1 and fewer than 10% of patients had a CCS > 3. Compared with patients who had no residual congestion (CCS = 0) at discharge, those with a CCS > 3 had an independently increased risk of the composite outcome of all-cause mortality or HF hospitalization at both 30 days and throughout the 9.9-month follow-up

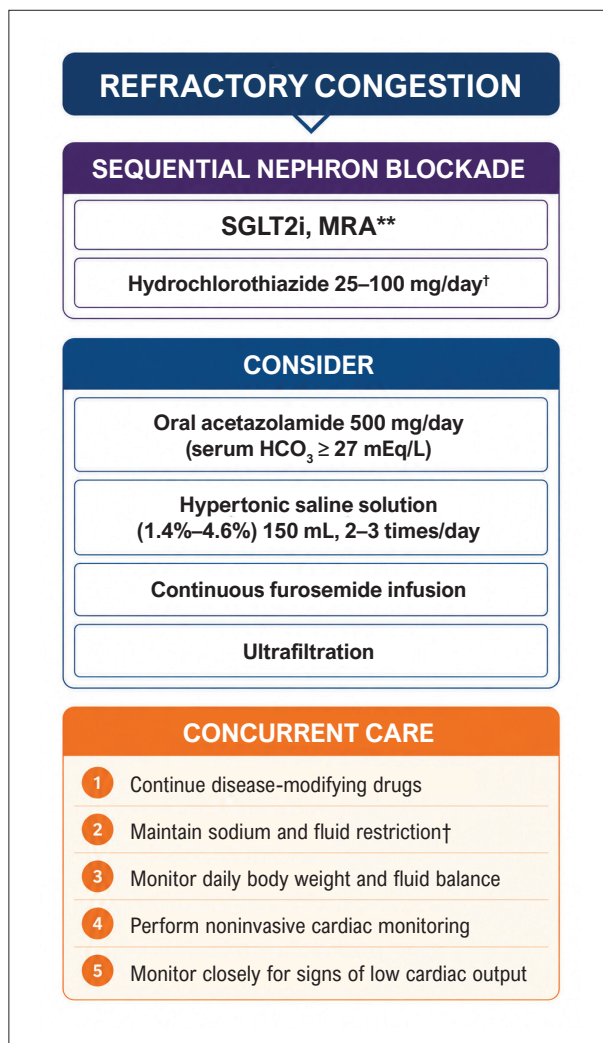


Figure 7.7 – Interventions for the management of refractory congestion. *Loop diuretics exhibit a threshold effect, below which there is no meaningful diuretic response. Above this threshold, the response is dose-dependent, with proportional increases in natriuresis and diuresis. In clinical practice, when the response to diuretic therapy is insufficient, increasing the diuretic dose is generally more effective than repeating the same dose at shorter intervals; **In the ATHENA-HF trial, high-dose spironolactone (100 mg/day) was not superior to the standard dose (25 mg/day) in improving decongestion in patients with decompensated heart failure. However, this dose may be considered for the management of hypokalemia associated with decongestion; †In the CLOROTIC trial, hydrochlorothiazide dosing was adjusted according to estimated glomerular filtration rate (eGFR): 25 mg/day for eGFR >50 mL/min, 50 mg/day for eGFR 20–50 mL/min, and 100 mg/day for eGFR <20 mL/min; ‡The FRESH-UP trial demonstrated that a daily fluid intake of approximately 1,800 mL did not result in significant differences in Kansas City Cardiomyopathy Questionnaire (KCCQ) scores compared with fluid restriction to ≤1500 mL/day. MRA: mineralocorticoid receptor antagonist; FB: fluid balance; HCO₃⁻: bicarbonate; SGLT2i: sodium–glucose cotransporter 2 inhibitor.

Table 7.5 – Recommendations for the management of refractory congestion in heart failure

Recommendation	Strength of recommendation	Certainty of evidence
In patients with persistent signs of congestion, we recommend IN FAVOR OF progressively increasing the furosemide dose by doubling it, with administration either as intermittent boluses or continuous infusion, until the maximum furosemide dose is reached.	STRONG	HIGH
In patients with congestion refractory to loop diuretic monotherapy, we recommend IN FAVOR OF combining diuretics with different mechanisms of action, such as thiazide diuretics or carbonic anhydrase inhibitors.	STRONG	MODERATE
In patients with congestion refractory to optimized medical therapy, including combination diuretic therapy, we recommend IN FAVOR OF the use of renal replacement therapy with ultrafiltration in selected cases.	STRONG	MODERATE
In patients with congestion refractory to conventional diuretic therapy, with or without associated hyponatremia, we recommend IN FAVOR OF the use of hypertonic saline combined with loop diuretics, particularly in centers experienced with this strategy, to enhance the diuretic response.	WEAK	LOW

HF: heart failure.

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Chart 7.4 – Congestion score from the EVEREST trial

Signs and symptoms	Score			
	0	1	2	3
Dyspnea	None	Seldom	Frequent	Continuous
Orthopnea	None	Seldom	Frequent	Continuous
Fatigue	None	Seldom	Frequent	Continuous
Jugular venous distention (cm H ₂ O)*	≤ 6	6–9	10–15	≥ 15
Rales	None	Bases	< 50% lung zones	≥ 50% lung zones
Edema	Absent/trace	Slight	Moderate	Marked

The congestion score from the EVEREST trial is calculated by summing the individuals scores for each of the 6 signs/symptoms of heart failure. *These items are part of the composite congestion score (orthopnea, jugular venous distention, edema). Adapted from Ambrosy et al.⁴⁴⁷

period. The congestion score from the EVEREST trial has been recently recommended as a tool for assessing decongestion in a European Society of Cardiology consensus statement.

7.6.2. Monitoring with Point-of-care Ultrasound

Clinical assessment based solely on physical examination may have limited sensitivity for detecting pulmonary congestion and/or hypervolemia in a proportion of patients with DHF.^{61,446,449,450} Accurate assessment of these findings is essential for the optimal treatment of patients with DHF, as congestion is the main determinant of symptoms, hospitalization, and prognosis.

LUS performed with a handheld probe has emerged as a rapid (< 5 minutes), inexpensive, and bedside diagnostic tool that provides information complementary to the physical examination for the detection of pulmonary congestion. In patients hospitalized for suspected DHF, LUS has demonstrated high diagnostic accuracy, with a sensitivity of 94%–97% and a specificity of 97%, outperforming conventional diagnostic tests (chest radiography and NP measurements).^{451–454}

In general, LUS protocols for the evaluation of patients with DHF assess multiple lung zones for the presence of B-lines – vertical comet-tail artifacts that originate from the pleural line, extend to the bottom of the screen without fading, and correlate with increased extravascular lung water.⁴⁵²

Patients with an increased number of B-lines at hospital admission for DHF are at higher risk of events, independently of the degree of cardiac dysfunction or other manifestations of congestion.⁴⁵⁵

Conversely, B-lines may decrease rapidly in patients who respond well to diuretic therapy, and LUS can be used to guide and titrate decongestive therapy, potentially contributing to a shorter hospital stay.^{456,457}

Therefore, residual pulmonary congestion detected by LUS during pre-discharge is strongly associated with adverse outcomes. In a systematic review including 13 studies, the finding of ≥ 15 B-lines on 28-zone LUS at

discharge identified patients at a 5-fold higher risk of HF readmission or death.⁴⁵⁸

However, there is no universally accepted consensus regarding the optimal number of lung zones to be examined or the congestion thresholds with prognostic significance when performing LUS before hospital discharge. The most commonly used protocols evaluate 4, 8, or 28 lung zones. A lung zone is considered positive for congestion when it demonstrates ≥ 3 B-lines. Prospective studies examining the association between the presence of B-lines and post-discharge prognosis in patients hospitalized for DHF, using a 4-zone imaging protocol, have shown that a total of ≥ 7 B-lines identifies patients with significant pulmonary congestion and a worse post-discharge prognosis.⁴⁵⁹

When an 8-zone lung ultrasound protocol is used, a patient is considered positive when at least one positive zone is identified in each hemithorax.⁴⁶⁰

In another study using the 28-zone protocol, the threshold to identify a worse prognosis was a total of ≥ 15 B-lines.⁴⁶¹

IVC ultrasound can also be performed easily at the bedside using portable devices, providing a reliable estimate of right atrial pressure and changes in volume status during treatment. A persistently dilated IVC (> 20 mm) with reduced inspiratory collapsibility (< 50%) before hospital discharge is associated with an increased risk of readmission during the vulnerable phase. It is important to emphasize that a dilated IVC is a marker of systemic congestion, rather than pulmonary congestion.⁴⁶²

Nevertheless, IVC assessment has limitations, as dilation may also occur in conditions such as pulmonary hypertension or in patients receiving PPV. To improve the accuracy of volume status assessment and to better characterize the effects of elevated venous pressure on multiple organs, the Venous Excess Ultrasound (VExUS) grading system was developed.⁴⁶³ This system evaluates the severity of venous congestion by assessing not only the IVC but also the hepatic, portal, and intrarenal veins. When the IVC diameter exceeds 2 cm,

pulsed-wave Doppler patterns of these veins are incorporated into the evaluation. The VExUS protocol grades ultrasound and Doppler findings on a 4-point scale, ranging from grade 0 (no congestion) to grade 3 (severe congestion).⁴⁶³

Table 7.6 summarizes the recommendations for the use of decongestion monitoring methods during hospitalization for DHF.

7.7. Oxygen Supplementation and/or Ventilatory Support

In patients with DHF who present with hypoxemia, supplemental oxygen is recommended.⁴ In the absence of hypoxemia, supplemental oxygen should be avoided, as evidence indicates that high concentrations of inspired oxygen may produce adverse hemodynamic effects (reduced cardiac output and increased SVR) in patients with HFrEF.⁴⁶⁴ NIPPV is also beneficial in patients with DHF requiring hospitalization who experience significant respiratory distress. In patients with pulmonary edema, NIPPV has been shown to provide more rapid relief of dyspnea and correction of metabolic disturbances than oxygen therapy alone.^{417,465}

A meta-analysis by Vital et al., including 32 studies, demonstrated that NIPPV reduces respiratory distress and the need for endotracheal intubation in patients with pulmonary edema.⁴⁷⁶ NIPPV should be initiated as early as possible in patients with respiratory distress (respiratory rate > 25 breaths/min and SpO₂ < 90%).⁴ Patients receiving NIPPV require continuous monitoring of vital signs and periodic assessment of gas exchange. If respiratory failure progresses despite therapy, endotracheal intubation is recommended.

Table 7.7 summarizes the recommendations for oxygen supplementation or ventilatory support in patients with DHF. In addition, venous thromboembolism (VTE) prophylaxis is recommended for all patients hospitalized for DHF unless contraindications to its use are present.⁴

7.8. Vasodilators

Intravenous vasodilators, particularly nitrates and sodium nitroprusside, dilate both venous and arterial vessels, thereby reducing venous return to the heart, relieving congestion, decreasing afterload, increasing stroke volume, and, consequently, improving symptoms. Nitrates act predominantly on the peripheral venous circulation, whereas sodium nitroprusside provides a more balanced arterial and venous vasodilatory effect.^{467,468} Because of these mechanisms of action, intravenous vasodilators may be more effective than diuretics in patients with acute pulmonary edema caused by increased afterload and redistribution of fluid into the pulmonary circulation, with no to minimal fluid collection.^{404,469-471} However, 2 recent RCTs comparing usual care with early intensive and sustained vasodilator therapy failed to demonstrate a clinical benefit of intravenous vasodilators over high-dose diuretics.^{472,473} Therefore, no recommendation can currently be made in favor of a vasodilator-based strategy over usual care to improve major clinical outcomes.

However, intravenous vasodilators might be considered to relieve symptoms of pulmonary congestion in patients with DHF when SBP exceeds 110 mm Hg. Therapy should be initiated at low doses and titrated according to clinical

Table 7.6 – Recommendations for the use of decongestion monitoring methods during hospitalization for decompensated heart failure

Recommendation	Strength of recommendation	Certeza da evidência
We recommend IN FAVOR OF the use of clinical congestion scores to monitor decongestion throughout hospitalization for decompensated heart failure.	STRONG	MODERATE
We recommend IN FAVOR OF the use of point-of-care ultrasound, when available, to provide more accurate monitoring of decongestion during hospitalization for DHF and to optimize volume management	STRONG	MODERATE

Table 7.7 – Recommendation for oxygen supplementation or ventilatory support in patients hospitalized for DHF

Recommendation	Strength of recommendation	Certainty of evidence
In patients with SpO ₂ < 90% or PaO ₂ < 60 mm Hg, we recommend IN FAVOR OF supplemental oxygen to correct hypoxemia.	STRONG	LOW
In patients with a respiratory rate > 25 breaths/min and SpO ₂ < 90%, we recommend IN FAVOR OF early initiation of noninvasive positive-pressure ventilation to reduce respiratory distress and the need for endotracheal intubation.	STRONG	MODERATE
In patients with progressive respiratory failure despite supplemental oxygen and noninvasive positive-pressure ventilation, we recommend IN FAVOR OF endotracheal intubation.	STRONG	LOW

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response and BP control. Nitrates are generally administered as an initial bolus followed by continuous intravenous infusion, although repeated bolus administration is also an acceptable strategy. In patients with severe hypertension and acute pulmonary edema, nitroglycerin may be administered as 1–2 mg intravenous boluses.⁴⁷⁰ Caution should be taken to prevent hypotension resulting from excessive reductions in preload and afterload. For this reason, intravenous vasodilators should be used with particular caution in patients with LV hypertrophy and/or severe aortic stenosis (AS). Nevertheless, favorable effects have been reported in patients with LV systolic dysfunction and AS when vasodilators are administered under careful hemodynamic monitoring.

7.9. Inotropic Agents

The increasing incidence of cases of HF, along with advances in the treatment of chronic HF, has resulted in a growing number of patients progressing to advanced

HF, leading to multiple hospitalizations and progressive multisystem dysfunction.^{474,475}

In this setting, particularly in patients with DHF and severe hemodynamic compromise, symptomatic hypotension, low cardiac output with end-organ dysfunction, or cardiogenic shock (CS), treatment with inotropic agents or other vasoactive drugs is indicated.^{476,477}

Chart 7.5 summarizes the main characteristics of the inotropic agents used in the treatment of DHF with low cardiac output. To date, there is no evidence demonstrating a survival benefit associated with the use of inotropic agents, and some cohort studies have reported an association with increased mortality.^{478,479} Therefore, the primary goal of inotropic therapy is to improve cardiac output and maintain adequate tissue and organ perfusion. These agents should be administered at the lowest effective dose and for the shortest possible duration required to achieve hemodynamic stabilization.

Table 7.8 summarizes the recommendations for the use of inotropic agents in DHF

Chart 7.5 – Key characteristics of the inotropic agents most commonly used in the treatment of decompensated heart failure with low cardiac output

	Dobutamine	Milrinone	Levosimendan
Mechanism of action	β 1- and β 2-adrenergic agonist	Phosphodiesterase-3 inhibitor (inotropism + lusitropism)	Calcium sensitizer (inotropism without $\uparrow$ VO_2)
Pharmacologic class	Synthetic catecholamine	Phosphodiesterase inhibitor	Calcium sensitizer
Initial dose	0.5–1 $\mu\text{g/kg/min}$	50 $\mu\text{g/kg}$ over 10 min (optional bolus)	6–12 $\mu\text{g/kg}$ (optional bolus)
Maintenance dose	2–20 $\mu\text{g/kg/min}$ (up to 40 $\mu\text{g/kg/min}$)	0.375–0.75 $\mu\text{g/kg/min}$ (continuous)	0.1–0.2 $\mu\text{g/kg/min}$ (up to 0.4 $\mu\text{g/kg/min}$)
Duration of action	Rapid (minutes) Reversible	Intermediate Reversible	Prolonged (up to 24–48 h)
Inotropic effect	+++ (strong)	++ (moderate)	++ to +++ (strong)
Vasodilatory effect	+ (mild)	++ to +++ (strong)	++ (moderate)
Lusitropic effect	- (absent)	+++ (strong)	++ (moderate)
Myocardial O_2 consumption	$\uparrow\uparrow$ (increased)	$\downarrow$ (reduced)	$\rightarrow$ (unchanged)
Tachycardia	$\uparrow\uparrow$ (frequent)	$\uparrow$ (occasional)	$\uparrow$ (occasional)
Main indications	Decompensated HF Cardiogenic shock Weaning from mechanical circulatory support	Decompensated HF Cardiogenic shock Patients receiving beta-blockers Pulmonary hypertension	Decompensated HF Cardiogenic shock Weaning from mechanical circulatory support Patients receiving beta-blockers
Contraindications	Aortic/pulmonary stenosis Hypertrophic obstructive cardiomyopathy Uncorrected hypovolemia	Aortic/pulmonary stenosis Hypertrophic obstructive cardiomyopathy Uncorrected hypovolemia Severe renal failure	Severe hypotension Uncontrolled tachyarrhythmias Mechanical obstruction Severe aortic stenosis

Common adverse effects	Tachycardia Ventricular arrhythmias Hypertension/hypotension Angina Hypokalemia	Hypotension Supraventricular arrhythmias Ventricular arrhythmias Worsening LVOT obstruction	Hypotension Tachycardia Arrhythmias Headache Myocardial ischemia (rare)
Dose adjustment in renal failure	Not required	Major dose adjustment required	Minimal dose adjustment required
Mortality benefit	Not demonstrated	Not demonstrated (possible increase in some studies)	Mortality reduction in some studies
Advantages	• Rapid onset • Reversible • Easy titration • No renal dose adjustment	• Less tachycardia • Potent vasodilation • Lusitropism • Useful in beta-blockade	• Prolonged action • Without $\uparrow$ VO_2 • Potential mortality benefit • Improved LV function
Disadvantages	• $\uparrow$ myocardial VO_2 consumption • Frequent tachycardia • Arrhythmias • Short duration	• Risk of hypotension • Requires renal dose adjustment • Less inotropic than dobutamine • High cost	• Risk of hypotension • Limited availability • High cost
Preferred clinical scenario	Need for rapid adjustment Preserved kidney function Patients not receiving beta-blockers	Patients receiving beta-blockers Pulmonary hypertension Need for vasodilation Risk of tachyarrhythmia	Need for prolonged effect Concern about myocardial VO_2 consumption Potential mortality benefit Regional availability

LVOT: left ventricular outflow tract.

7.10. Vasopressors

In the setting of DHF – with severe hemodynamic compromise, profound hypotension, and critically impaired tissue and organ perfusion – as well as in CS, the use of vasopressor agents is indicated and necessary to maintain adequate tissue perfusion and sustain life.^{480,481} Chart 7.6 summarizes the main characteristics of vasopressor agents used in DHF. Therefore, in patients receiving, awaiting, or deemed ineligible for MCS or heart transplant, maintenance of hemodynamic stability with vasopressors, either alone or in combination with inotropic agents, is often required.⁴⁸²

Table 7.9 summarizes the recommendations for the use of vasopressor agents in DHF

7.11. Digitalis Glycosides

To date, no RCTs have specifically evaluated the role of digitalis glycosides in DHF. The DIG trial showed that digoxin reduced all-cause hospitalizations and HF hospitalizations, with a trend toward a decrease in the risk of death attributable to worsening HF.¹⁷³

Analyses from large registries and an international cohort have shown that digoxin was administered to 1 in 10 patients presenting to the emergency department with DHF due to AF with rapid ventricular response. These studies also identified that digoxin use after an episode of DHF was associated with certain clinical characteristics (AF, female sex, reduced LVEF,

absence of diabetes mellitus, and absence of CKD), but found no significant effect on 30-day mortality or 90-day clinical outcomes.^{485–484} Among older hospitalized patients with HFrEF receiving GDMT, discontinuation of pre-admission digoxin therapy was associated with worse clinical outcomes.⁴⁸⁶

In patients not previously receiving digoxin, an intravenous loading dose of 0.25–0.5 mg may be administered. However, patients with impaired or fluctuating renal function, older adults, individuals with low body weight, and women are at greater risk of digoxin toxicity and may require closer monitoring, including measurement of serum digoxin concentrations.⁴ In patients with AF and HF, digoxin is a reasonable option for rate control, either in combination with other rate-controlling agents or as monotherapy when other agents are not tolerated.⁴⁸⁷

Table 7.10 summarizes the recommendations for the use of digitalis glycosides in DHF

7.12. Opioids

Morphine and short-acting benzodiazepines (midazolam) have been evaluated in DHF because they may reduce anxiety and dyspnea and improve the vasoconstriction accompanying hypertensive crises.⁴⁸⁸ However, RCTs have not provided convincing evidence of clinical benefit for their routine use in patients with DHF. A meta-analysis including 152,859 patients found that morphine use in acute cardiogenic pulmonary edema (ACPE) was significantly associated with worse clinical outcomes.⁴⁸⁹

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Table 7.8 – Recommendations for the use of inotropic agents in decompensated heart failure

Recommendation	Strength of recommendation	Certainty of evidence
In patients with evidence of low cardiac output/hypoperfusion and systolic blood pressure <90 mm Hg, we recommend IN FAVOR OF the use of beta-adrenergic inotropic agents to increase cardiac output and peripheral tissue perfusion.	STRONG	LOW
We recommend AGAINST the routine use of inotropic agents for the treatment of patients with decompensated heart failure.	STRONG	LOW

Chart 7.6 – Main pharmacologic characteristics of the vasopressor agents most commonly used in decompensated heart failure

Agent	Primary adrenergic receptor activity	Pharmacologic effect	Continuous infusion dose	Adverse effect
Norepinephrine	α1 agonist β1 agonist	Vasoconstrictor	0.2–1.0 µg/kg/min	Tachyarrhythmias, hypertension, tissue necrosis
Epinephrine	α1 agonist β1 agonist β2 agonist	Inotropic Chronotropic Vasoconstrictor	0.05–0.5 µg/kg/min	Tachyarrhythmias, headache, hypertension

Table 7.9 – Recommendations for the use of vasopressor agents in decompensated heart failure

Recommendation	Strength of recommendation	Certainty of evidence
In patients with severe hemodynamic compromise and profound hypotension resulting in impaired tissue and organ perfusion, we recommend IN FAVOR OF the use of a vasopressor agent.	STRONG	LOW

The MIMO trial, which compared midazolam with morphine in patients presenting to the emergency department with ACPE, found no significant difference in in-hospital mortality. However, the morphine group experienced a significantly higher rate of serious adverse events at 30 days.⁴⁹⁰ These findings should be interpreted with caution because the trial was terminated prematurely by the Data and Safety Monitoring Board (DSMB), resulting in loss of statistical power to detect differences in the primary outcome due to failure to achieve the planned sample size.⁴⁹¹

A meta-analysis including 1180 records concluded that the use of opioids for the treatment of breathlessness in HF is questionable and should be reserved as a last-line option when other therapies have failed or in emergency situations.⁴⁹² Therefore, routine opioid use is not recommended, given the risk of adverse effects, including nausea, hypotension, bradycardia, and respiratory depression, as well as ongoing concerns regarding a potential increase in mortality.⁴⁹³

Table 7.11 summarizes the recommendations for the use of opioids in DHF

7.13. Thromboembolism Prophylaxis

VTE prophylaxis is recommended for patients hospitalized for DHF. Available options include enoxaparin, unfractionated

heparin, and rivaroxaban, all of which have been shown to reduce radiographic evidence of venous thrombosis. However, their effects on mortality and rates of clinically significant pulmonary embolism remain uncertain.⁴⁹⁴

In patients with DHF, the decision to initiate anticoagulant therapy is guided primarily by the presence of specific risk factors, such as AF or a history of thromboembolic events. Anticoagulation is recommended for patients with HF and AF using the CHA₂DS₂-VASc score to estimate stroke risk and guide treatment decisions.⁴⁹⁴ For patients with HF who remain in sinus rhythm, routine anticoagulation is generally not recommended, as current evidence does not demonstrate a mortality benefit and indicates an increased risk of bleeding.⁴⁹⁵⁻⁴⁹⁷

The decision to prescribe anticoagulation in patients with HF and sinus rhythm should be individualized, carefully balancing the potential risks and benefits, particularly the risk of major bleeding.^{495,496}

Overall, although anticoagulation is clearly indicated for patients with DHF and AF, its use in those in sinus rhythm should be carefully considered and is generally not recommended unless another established indication for anticoagulation is present.

Table 7.12 summarizes the recommendations for anticoagulation in patients with DHF

Table 7.10 – Recommendations for the use of digitalis glycosides in decompensated heart failure

Recommendation	Strength of recommendation	Certainty of evidence
In patients with DHF and atrial fibrillation with rapid ventricular response, we recommend IN FAVOR OF the use of digitalis glycosides for rate control.	WEAK	LOW

Table 7.11 – Recommendations for the use of opioids in decompensated heart failure

Recommendation	Strength of recommendation	Certainty of evidence
In patients with decompensated heart failure, we recommend AGAINST the routine use of opioids, except in selected patients with severe/intractable pain or anxiety.	STRONG	LOW

Table 7.12 – Recommendation for anticoagulation in decompensated heart failure

Recommendation	Strength of recommendation	Certainty of evidence
In patients without contraindications to anticoagulation, we recommend IN FAVOR OF the use of venous thromboembolism prophylaxis with low-molecular-weight heparin or unfractionated heparin to reduce the risk of deep vein thrombosis and pulmonary embolism.	STRONG	HIGH

7.14. Cardiorenal Syndromes in Decompensated Heart Failure and Their Management

7.14.1. Cardiorenal Syndrome in Decompensated Heart Failure

CRS is one of the greatest challenges in the management of DHF. It results from the bidirectional interaction between the heart and kidneys, in which systemic and venous congestion, reduced cardiac output, and neurohormonal activation contribute to the progressive deterioration of renal function.

Worsening renal function (WRF), which can be defined as an increase in serum creatinine of >0.3 mg/dL from baseline, is a frequent finding at hospital admission in patients with DHF, occurring in 30%–50% of cases. WRF is a marker of poor prognosis and is associated with increased mortality and higher rates of rehospitalization for DHF.⁴⁹⁸

Although renal hypoperfusion plays a role in the mechanism of WRF upon admission of patients with DHF, its principal determinant is elevated CVP and renal venous pressure, leading to renal congestion and impaired glomerular filtration.⁴⁹⁹

Thus, the recommended initial therapeutic approach for patients with WRF without signs of low cardiac output is decongestive therapy using effective doses of intravenous furosemide. In this setting, increased intra-abdominal pressure due to large-volume ascites may further contribute to WRF. When present, therapeutic paracentesis is indicated, offering more comfort to the patient.⁵⁰⁰⁻⁵⁰²

7.14.2. Renal Function Trajectories During Decompensated Heart Failure Treatment

In the setting of DHF, the response to diuretic therapy is a critical determinant of the patient's clinical trajectory. The ability to remove excess volume without inducing renal deterioration defines prognosis, length of hospital stay, and the risk of recurrence. Five distinct phenotypes of response to diuretic therapy during hospitalization have been described, each with unique pathophysiological and prognostic implications and management considerations. These response phenotypes are summarized in Chart 7.7 and Figure 7.8. Early recognition of these phenotypes enables a more personalized approach to DHF complicated by CRS. Whereas some patients may benefit from intensification of diuretic therapy or the addition of vasodilators, others require alternative strategies, such as UF, hemodynamic optimization guided by invasive monitoring, or even temporary renal replacement therapy.

Thus, the clinical trajectory of CRS is not uniform but rather reflects the dynamic interplay among congestion, diuretic responsiveness, and preservation of renal function, as represented by the 5 clinical phenotypes.

7.15. Other Presentations of Decompensated Heart Failure

7.15.1. Acute Pulmonary Edema

Acute pulmonary edema is a major cause of unplanned hospitalization, particularly among older adults (> 65 years of age).^{1,4,11,402,404,406,408-414,503,504}

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Chart 7.7 – Characterization of clinical phenotypes according to renal function trajectory and treatment response in patients with decompensated heart failure

1. Responder: adequate diuresis with preserved renal function

- **Characteristics:** Adequate response to diuretic therapy, with relief of congestion symptoms and stable renal function.
- **Trajectory:** This represents the ideal scenario and is associated with more favorable outcomes, shorter hospital stays, and a lower risk of readmission.
- **Predominant mechanism:** Volume overload without substantial structural renal impairment, with reversible renal dysfunction after decongestion.
- **Management:** Maintain the current diuretic regimen until the predefined target weight is achieved, signs and symptoms of congestion resolve, and clinical status improves.

2. Pseudo-worsening renal function: adequate diuretic response with worsening renal function (increased serum creatinine)

- **Characteristics:** Substantial reduction in congestion, yet accompanied by an increase in serum creatinine or a decrease in glomerular filtration rate.
- **Trajectory:** This is considered the “paradoxical” form of cardiorenal syndrome. Despite the clinical improvement in congestion, laboratory evidence of worsening renal function is not associated with increased long-term mortality.
- **Predominant mechanism:** Reduction in renal venous filling pressure, yet accompanied by decreased renal perfusion due to relative hypovolemia or intrarenal vasoconstriction.
- **Management:** Maintain the current diuretic regimen until the predefined target weight is achieved, signs and symptoms of congestion resolve, and clinical status improves.

3. Nonresponder: inadequate diuretic response with preserved renal function

- **Characteristics:** Increasing doses of diuretics are required to achieve an adequate diuretic response, but without a substantial increase in serum creatinine.
- **Trajectory:** Patients still have residual congestion and are at increased risk of persistent symptoms and hospital readmission, despite the absence of immediate renal deterioration.
- **Predominant mechanism:** Diuretic resistance related to neurohormonal activation, tubular dysfunction, or irregular intestinal absorption of diuretics.
- **Management:** Follow the intravenous furosemide treatment algorithm for decompensated heart failure, generally by doubling the furosemide dose. Once the maximum intravenous furosemide dose has been reached, combination diuretic therapy may be required. Intravenous vasodilators may also be initiated or up-titrated, and ultrafiltration may be considered in selected cases.

4. Warm profile: inadequate diuretic response with worsening renal function but no evidence of low cardiac output/tissue hypoperfusion

- **Characteristics:** Patients exhibit signs of (particularly systemic) hypervolemia, without adequate decongestion and with progressive deterioration of renal function. However, there is no clinical evidence of low cardiac output/tissue hypoperfusion on noninvasive bedside assessment (“warm profile” in the Stevenson classification). Right ventricular failure, pulmonary hypertension, and more severe tricuspid regurgitation are common in these patients.
- **Trajectory:** Patients still have signs of (particularly systemic) hypervolemia and are at increased risk of persistent congestive symptoms and hospital readmission. Renal deterioration is associated with a worse prognosis.
- **Predominant mechanism:** Worsening renal function results from decreased renal perfusion despite the absence of signs of low cardiac output on physical examination. The principal mechanism is a mismatch between right-sided preload, characterized by hypervolemia and elevated filling pressures, and left-sided preload, which may have reduced filling pressures. This mismatch is associated with increased pulmonary arteriolar resistance.
- **Management:** Management is similar to that of profile C and may include intravenous vasodilators or inotropic agents.

5. Profile C: inadequate diuretic response with worsening renal function and evidence of low cardiac output/tissue hypoperfusion

- **Characteristics:** Absence of adequate decongestion, associated with progressive deterioration of renal function.
- **Trajectory:** This phenotype is associated with the worst prognosis, including high mortality and an increased likelihood of requiring renal replacement therapy or advanced circulatory support, either pharmacologic or mechanical.
- **Predominant mechanism:** A combination of diuretic resistance with irreversible structural or functional renal injury, often occurring in the setting of refractory congestion and poor tissue perfusion.
- **Management:** Treat according to profile C. Intravenous inotropic agents or vasodilators should be added according to the patient's hemodynamic status. Management is generally conducted in an intensive care unit.

Patients with persistent congestion/hypervolemia				
Worsening renal function	Diuretic response	Low cardiac output	Clinical phenotype	Approach
–	+	–	Responder	Continue diuretic therapy
+	+	–	Pseudo-WRF	Continue diuretic therapy
–	–	–	Nonresponder	Diuretic up-titration Combination therapy Ultrafiltration
+	–	–	Warm profile	IV vasodilator Inotropic agent
+	–	+	Profile C	ICU IV vasodilator Inotropic agent

Figure 7.8 – Summary of the clinical phenotypes of renal function trajectories in patients with decompensated heart failure and the management strategies to be considered. ICU: intensive care unit; IV: intravenous; HF: heart failure; WRF: worsening renal function.

It is a severe clinical condition associated with an estimated in-hospital mortality of 4% to 10%. Rehospitalization rates are also high, ranging from 15% within the first month to approximately 50% at 6 months. Approximately 1 in 3 patients hospitalized for acute pulmonary edema dies within 1 year.^{4,406,504}

Acute pulmonary edema is characterized by an abrupt increase in PCWP resulting in acute ventricular failure (systolic and diastolic) or severe MR.⁵⁰⁴⁻⁵⁰⁷

Clinically, patients manifest pulmonary congestion through dyspnea, orthopnea, tachypnea (respiratory rate > 25 breaths/min), increased work of breathing, hypoxemia, and respiratory failure.^{1,4,504} The underlying pathophysiological mechanism is acute LV failure leading to elevated PCWP.

Early recognition is mandatory. Clinical history, physical examination, chest radiography, LUS, and NT-proBNP measurement are widely available tools that facilitate diagnosis.^{464,504,507} In this context, it is important to note that BNP levels < 100 pg/mL or NT-proBNP levels < 300 pg/mL have a high negative predictive value.

The immediate therapeutic goals are to restore adequate tissue oxygenation, relieve symptoms of pulmonary congestion, and achieve and adequate double product (especially BP). Oxygen supplementation (invasive or noninvasive), diuretics, and vasodilators constitute the cornerstone of treatment.^{504,508}

7.15.2. Isolated Right Ventricular Failure

Isolated RV failure may occur in a variety of clinical settings, and its diagnosis is frequently overlooked because its manifestations are often masked by concomitant conditions.⁵⁰⁹ A common example is the perioperative period of complex cardiac surgery, in which the presentation of arterial hypotension and limited monitoring is interpreted as isolated vasoplegia. In patients with pulmonary embolism, obstructive shock may be misinterpreted as being secondary to hypoxemia. In severe acute respiratory distress syndrome (ARDS), hypoxemia and hypercapnia may precipitate RV failure, producing a clinical presentation that mimics obstructive shock caused by pulmonary embolism.^{509,510} Therefore, accurate etiologic diagnosis, comprehensive echocardiographic assessment, and, when appropriate, invasive hemodynamic monitoring are essential for selecting the optimal supportive strategy and establishing prognosis.^{509,511}

It is important to highlight that the RV is highly sensitive to changes in both preload and afterload. Because it normally functions as a low-pressure chamber, optimization of preload and afterload can produce substantial improvements in RV performance, even in the presence of significant dysfunction.^{509,511} Particular emphasis should be placed on the pulmonary artery pulsatility index (PAPi), a hemodynamic parameter with important prognostic value.⁵¹⁰ PAPi reflects the ability of the RV to generate pressure against the pulmonary vascular bed while accommodating venous preload.⁵⁰⁹

In addition, LV function exerts a significant influence on RV contractility because, morphologically, the 2 ventricles share transverse myocardial fibers, creating both mechanical and electrical ventricular interdependence.⁵⁰⁹ Conversely, intrinsic RV contractile function depends primarily on longitudinal myocardial fiber shortening, particularly the excursion of the tricuspid annulus. Therefore, RV longitudinal strain (RVLS) measured by echocardiography is an important prognostic marker.⁵¹¹

The different etiologies of acute RV dysfunction include pulmonary embolism, cardiac tamponade, RV infarction, multiple cardiomyopathies, and RV dysfunction secondary to implantation of an LV assist device (LVAD). Primary isolated RV graft failure is also a recognized complication after heart transplant, typically associated with perioperative pulmonary hypertension, congenital cardiac anatomical abnormalities requiring surgical adaptation, such as a persistent left superior vena cava, or pulmonary artery reconstruction. In addition, combined valve surgery complicated by pulmonary arterial hypertension, in the setting of hypervolemia and/or reoperation for mitral prosthetic valve dysfunction, may result in acute RV maladaptation and failure, as well as in unsuccessful adaptation after complex tricuspid valve repair.

Management requires assessment of disease severity, identification of precipitating factors, and volume optimization. Strategies aimed at reducing RV afterload and improving pulmonary blood flow should be considered, including the use of inodilators such as milrinone and inhaled nitric oxide. In postoperative patients, measures to reduce intrathoracic pressure, including early extubation when clinically feasible, may further improve RV performance.

Low-dose epinephrine administered predominantly for its beta-adrenergic effects (0.03–0.1 µg/kg/min) may enhance longitudinal RV contractility.⁵¹² In patients with a high vasoactive-inotropic score and clear evidence of RV failure, venoarterial extracorporeal membrane oxygenation (VA-ECMO) should be considered. Alternatively, right atrial cannulation with return to the pulmonary artery (Oxy-RVAD configuration) might be considered.⁵¹³

7.15.3. Cardiogenic Shock

CS remains a clinical presentation associated with high mortality. It is estimated to occur in approximately 10% of patients with myocardial infarction and accounts for nearly 50% of early deaths in this population.⁵¹⁴ Similar rates have been reported in patients with other causes of acute cardiomyopathy.^{515–517} These findings underscore the importance of implementing structured, disease-specific systems of care that facilitate early diagnosis and timely initiation of appropriate hemodynamic support. Therefore, the recommendations continue to follow the organizational framework established in the 2018 Guideline, with the development of dedicated shock teams and the adoption of the Society for Cardiovascular Angiography and Interventions (SCAI) classification of CS,⁵¹⁸ aiming to standardize the assessment of CS severity while recognizing cardiac arrest as a major modifier of prognosis. The DanGer Shock trial⁵¹⁴ has substantially influenced the design of clinical studies in

CS by excluding patients who experienced cardiac arrest, highlighting an important source of bias in many previously conducted RCTs.^{519,520}

The phenotypic characterization of CS using emerging markers of ventricular dysfunction has become an area of increasing interest.^{510,521,522} These include cardiac power output (CPO), PAPI, and the aortic pulsatility index (API), all of which may help guide the selection of the most appropriate MCS strategy and assess its potential impact.⁵¹⁶ This topic is discussed in greater detail in the section on temporary MCS. Future advances in the management of CS are likely to focus on multiplatform support strategies and on redefining primary clinical outcomes to evaluate combinations of therapeutic interventions rather than isolated treatments.^{510,517,522} Achieving these goals requires specialized training to ensure rapid and accurate interpretation of each patient's hemodynamic profile. In many cases, diagnosis is established using invasive hemodynamic assessment performed in a controlled environment, such as the cardiac catheterization laboratory. As part of shock team activation, this approach may facilitate the implementation of the most appropriate circulatory support, preventing cardiac arrest or hemodynamic deterioration during the subsequent hours. A similar strategy applies in the operating room, where activation of the shock team and enhanced hemodynamic monitoring can enable prompt, targeted interventions and prevent clinical deterioration through more precise phenotypic characterization of CS.^{509,517,522}

In the management of CS, invasive hemodynamic monitoring with a pulmonary artery catheter should be considered early, particularly in the presence of diagnostic uncertainty, evidence of impending organ dysfunction, or an inadequate response to initial therapy. Although its use has historically been controversial, growing evidence suggests that pulmonary artery catheterization may improve clinical outcomes in patients with CS.^{517,522} Vasoactive agents remain the fastest and most readily available means of providing circulatory support. The inotropic effect helps offset the reduction in cardiac output caused by increased afterload. However, high doses are associated with worse outcomes owing both to the severity of the underlying hemodynamic compromise and to their direct effect of increasing myocardial oxygen demand. Evidence comparing vasopressors in patients with shock of any etiology remains limited; therefore, treatment decisions should be guided by clinical judgment and the patient's hemodynamic profile. The lowest effective doses should be administered for the shortest possible duration. Contemporary practice increasingly favors combining multiple agents at lower doses, rather than escalating a single agent to extreme doses, to prevent ischemic vasoconstriction. Rapid escalation of catecholamine vasopressors (eg, increasing norepinephrine by > 0.2 µg/kg/min over 2 hours) without improvement in hypotension may indicate a vicious cycle of toxicity and resistance. Algorithms for titrating inotropic and vasopressor therapy have prognostic implications and may help guide treatment decision-making.

Table 7.13 summarizes the recommendations for the monitoring and management of CS in patients with DHF

Table 7.13 – Recommendations for the monitoring and management of cardiogenic shock

Recommendation	Strength of recommendation	Certainty of evidence
We recommend IN FAVOR OF continuous blood pressure monitoring using an arterial line.	STRONG	LOW
In patients with diagnostic uncertainty and/or an inadequate initial therapeutic response, we recommend IN FAVOR OF pulmonary artery catheter monitoring .	STRONG	MODERATE
We recommend IN FAVOR OF noninvasive hemodynamic monitoring (continuous noninvasive cardiac output monitoring, transthoracic and/or transesophageal echocardiography).	WEAK	MODERATE
We recommend IN FAVOR OF volume optimization with crystalloid solutions in the absence of signs of congestion.	STRONG	MODERATE
We recommend IN FAVOR OF the use of beta-adrenergic inotropic agents to achieve hemodynamic stabilization and improve cardiac output.	STRONG	MODERATE
We recommend IN FAVOR OF the use of vasopressors (preferably norepinephrine) to maintain end-organ perfusion, even when administered concomitantly with an inotropic agent.	WEAK	MODERATE
We recommend IN FAVOR OF coordinated multidisciplinary management using a dedicated shock team strategy.	STRONG	HIGH

7.16. Care Transition and Optimization of Pharmacologic Therapy During the Late Hospital Phase

Hospitalization for DHF represents a critical event in the natural history of the disease, with an in-hospital mortality rate of 10.9%, as well as high rates of rehospitalization at 90 days (24.3%) and 12 months (44.4%).²³ Furthermore, after an episode of DHF, the estimated risk of death is 6-fold higher during the first month after hospital discharge.⁵²³ Thus, 2 strategies are essential to minimize these adverse outcomes: ensuring effective decongestion and initiating or optimizing FMT during hospitalization. Several studies have demonstrated the benefits of foundational medical therapy (FMT) shortly after its initiation, supporting the initiation of these medications before hospital discharge if they are not already in use, as well as dose titration in hemodynamically stable patients without hypervolemia and with stable renal function.⁴⁴⁵⁻⁴⁶⁰

A recent analysis of the SOLVD trial demonstrated a reduction in the composite outcome of death or HF hospitalization with enalapril compared with placebo at 30 days after randomization.⁵²⁴ Similar early benefits have been reported with carvedilol, which reduced mortality and hospitalization within 14 to 21 days of treatment initiation,⁵²⁵ and with MRAs, which significantly reduced the composite of cardiovascular death or hospitalization at 19 days after treatment initiation.⁵²⁶

The PIONEER-HF trial demonstrated that initiation of sacubitril-valsartan in patients hospitalized for DHF after hemodynamic stabilization is both safe and effective. Compared with enalapril, sacubitril-valsartan produced a greater reduction in NT-proBNP, with benefits evident after 1 week of therapy. In addition, in-hospital initiation of sacubitril-valsartan reduced HF rehospitalization and the composite outcome of major clinical events (death, rehospitalization, ventricular assist device implantation, and listing for heart transplant) compared with enalapril.¹⁴³

Comparable benefits have also been demonstrated with SGLT2 inhibitors.

In the DAPA-HF trial, initiation of dapagliflozin was associated with a reduction in the composite outcome of cardiovascular death or worsening HF at 28 days after randomization.⁵²⁷ Similarly, in the EMPEROR-Reduced trial, empagliflozin reduced the risk of death, HF hospitalization, or an urgent visit requiring intravenous medications for worsening HF at 12 days after treatment initiation.⁵²⁸ The EMPA-RESPONSE-AHF and EMPULSE trials evaluating empagliflozin, together with the DICTATE-AHF trial evaluating dapagliflozin, further confirmed the efficacy and tolerability of SGLT2 inhibitors in patients hospitalized for DHF.^{148,528-530}

More recently, the STRONG-HF trial demonstrated that an intensive treatment strategy consisting of rapid up-titration of foundational medical therapy (FMT) and close outpatient follow-up during the first weeks after hospital discharge for DHF resulted in superior clinical outcomes compared with usual care. By day 90 after discharge, a higher proportion of patients in the high-intensity care group had been up-titrated to full doses of renin-angiotensin blockers, beta-blockers, and MRAs. They also experienced significant improvements in clinical and laboratory parameters, such as NYHA functional class and NT-proBNP levels. The intensive treatment strategy also significantly reduced the composite outcome of HF rehospitalization or all-cause mortality at 180 days (15.2% vs. 23.3%; $p = 0.0021$). These findings support the efficacy and feasibility of early, structured up-titration of GDMT in the post-discharge management of DHF.⁵³¹

During this stage of hospitalization, attention should also be directed toward the management of both cardiovascular and noncardiovascular comorbidities. Among these, iron deficiency is particularly relevant during the vulnerable post-discharge phase. The AFFIRM-AHF trial evaluated the effect of intravenous ferric carboxymaltose on

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outcomes in recently stabilized patients hospitalized for DHF with LVEF < 50% and iron deficiency, defined as a serum ferritin < 100 µg/L or 100–299 µg/L with transferrin saturation < 20%. Compared with placebo, ferric carboxymaltose significantly reduced the total number of HF hospitalizations (RR, 0.74; *p* = 0.013) and the composite of first HF hospitalization or cardiovascular death (HR, 0.80; *p* = 0.030), while demonstrating a favorable safety profile. These findings support correction of iron deficiency with ferric carboxymaltose after an episode of DHF, particularly to reduce the risk of recurrent hospitalizations.⁵³²

The IRONMAN trial evaluated the long-term effects of intravenous ferric derisomaltose in patients with HF, LVEF ≤ 45%, and iron deficiency. Compared with usual care, treatment with intravenous ferric derisomaltose was associated with a numerical reduction in HF hospitalizations and cardiovascular death over a median follow-up of 2.7 years. Although the study primarily enrolled outpatients, 14% of participants were recruited during a hospital admission for HF. These findings further support the benefits of correcting iron deficiency in patients with HF, not only in the short term but also in achieving sustained reductions in adverse clinical outcomes over time.⁵³³

Table 7.14 summarizes the recommendations for care transition during hospitalization for DHF.

7.17. Pre-Discharge Assessment, Planning, and Post-Discharge Care

Early readmissions after hospitalization for DHF are frequently associated with inadequate decongestion, failure to optimize or FMT, poor communication at the time of discharge, and limited access to prescribed medications and early outpatient follow-up. The 30-day period after hospital discharge has become recognized as a critical interval for monitoring clinical outcomes and implementing interventions aimed at improving both in-hospital treatment and care transition.⁵³⁴ This represents a particularly vulnerable phase, as more than half of all rehospitalizations occur within the first 15 days of discharge.⁵³⁵

Before hospital discharge, several criteria should be fulfilled to minimize adverse events during this vulnerable period. These include: resolution of the precipitating

factor; confirmation that the patient is free of congestion, receiving a stable dose of oral diuretics, and maintaining a stable body weight for at least 48 hours; stable renal function; no requirement for intravenous therapies for at least 48 hours; optimal GDMT; establishment of a follow-up plan, including outpatient reassessment within 7 to 14 days of discharge; and comprehensive patient education regarding HF and self-care measures before discharge. These educational interventions should include daily weight monitoring, dietary counseling with sodium and fluid restriction, avoidance of contraindicated medications, smoking and alcohol cessation, recommendations for physical activity and cardiac rehabilitation, and referral for appropriate vaccinations.^{536,537}

A recent scientific statement by the European Society of Cardiology (ESC) has proposed specific targets for decongestion and recommends that all patients undergo a comprehensive pre-discharge evaluation to ensure the absence of residual congestion using different methods encompassing 3 domains (Figure 7.9).⁴⁴⁸

- Clinical assessment, including the congestion score from the EVEREST trial (optimal = 0; acceptable = 1–2) and achievement of the patient's historical “dry” weight.
- Laboratory assessment, using NP levels, with targets of NT-proBNP < 1500 pg/mL or > 30% reduction from the admission value.
- Imaging assessment, including LUS and IVC ultrasound, with optimal and acceptable thresholds shown in the figure). A fundamental component of hospital discharge is the preparation of a detailed medical discharge summary for the outpatient care team. This document should clearly outline the patient's hospital course, the planned treatment strategy, therapeutic targets for further optimization, medication-related adverse effects and intolerances, in-hospital complications, and discharge body weight.

In addition, multidisciplinary care involving a cardiologist, nurse, dietitian, social worker, and psychologist, both before hospital discharge and throughout outpatient follow-up, can facilitate coordinated care across health care settings, helping to prevent recurrent hospitalizations and reduce

Table 7.14 – Recommendations for care transition during hospitalization for decompensated heart failure

Recommendation	Strength of recommendation	Certainty of evidence
We recommend IN FAVOR OF an intensive strategy of early initiation and rapid titration of foundational medical therapy (FMT) before hospital discharge and during follow-up visits after hospitalization for DHF to reduce the risk of HF rehospitalization or death	STRONG	MODERATE
In patients with HFrEF hospitalized for DHF who have iron deficiency (serum ferritin < 100 µg/L or serum ferritin 100–299 µg/L with transferrin saturation < 20%), we recommend IN FAVOR OF intravenous ferric carboxymaltose or ferric derisomaltose after clinical stabilization to reduce the risk of rehospitalization.	STRONG	MODERATE

HF: heart failure; HFrEF: heart failure with reduced ejection fraction.

mortality during the vulnerable post-discharge period.³⁹¹ An effective strategy includes a nurse-led telephone follow-up 7 days after hospital discharge to assess the patient's clinical status, with the possibility of medication adjustment, laboratory test requests, and scheduling of in-person

follow-up under physician supervision. This approach did not increase rehospitalization rates and reduced the need for in-person outpatient visits.^{391,538}

Table 7.15 summarizes the recommendations for the pre-discharge phase in patients hospitalized for DHF.

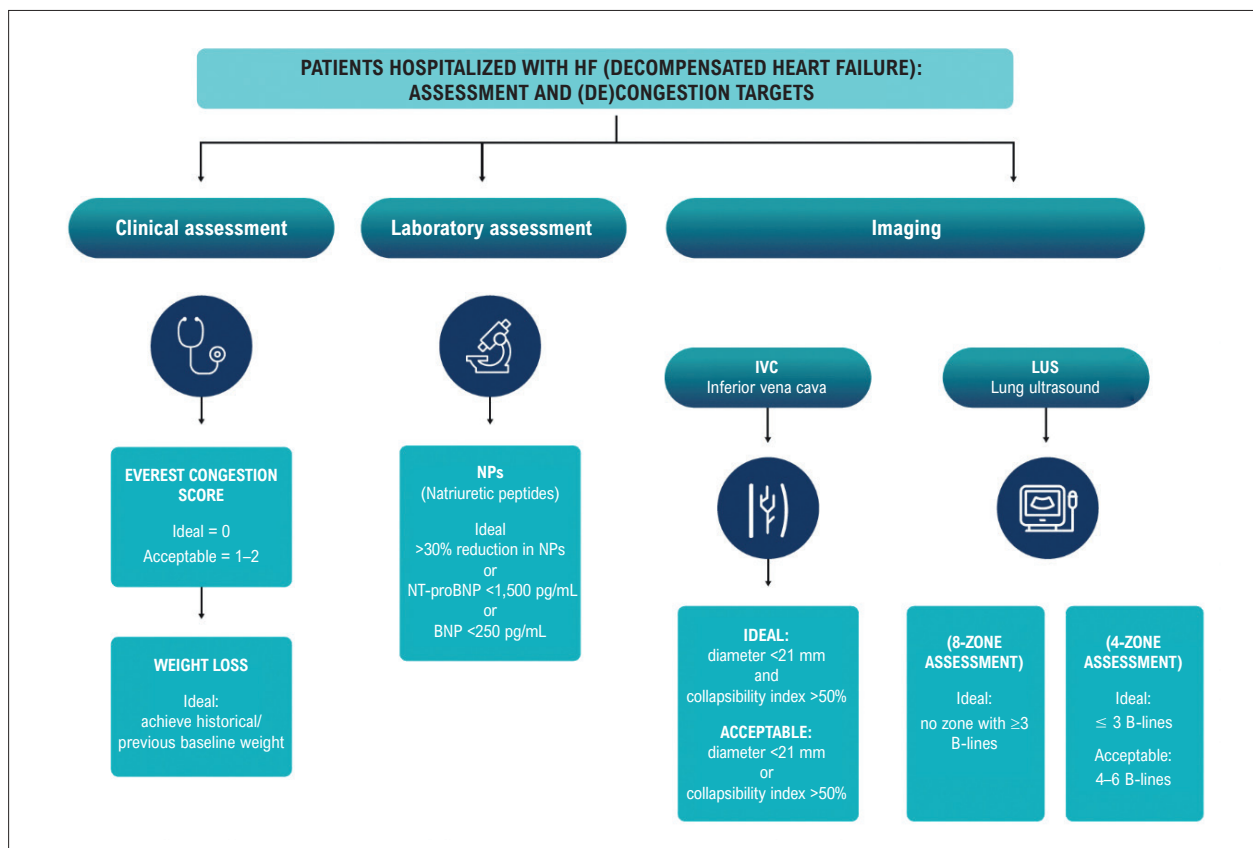


Figure 7.9 – Methods used to assess congestion and decongestion targets before hospital discharge for decompensated heart failure (DHF), including clinical congestion scores, biomarkers, and point-of-care ultrasound (POCUS).

Table 7.15 – Recommendations for pre-discharge assessment and post-discharge care

Recommendation	Strength of recommendation	Certainty of evidence
We recommend IN FAVOR OF ensuring complete decongestion before hospital discharge using clinical congestion scores and/or measurement of natriuretic peptides and/or point-of-care ultrasound (POCUS) to stratify prognosis and guide treatment optimization.	STRONG	MODERATE
We recommend IN FAVOR OF providing patient-centered discharge instructions with a clear transitional care plan before hospital discharge.	STRONG	MODERATE
We recommend IN FAVOR OF providing education on self-care and monitoring for signs of systemic congestion after hospital discharge.	STRONG	MODERATE
We recommend IN FAVOR OF clinical reassessment within 7 to 14 days of hospital discharge to optimize treatment and reduce rehospitalizations.	STRONG	MODERATE
We recommend IN FAVOR OF frequent multidisciplinary follow-up, including an intensive strategy of early initiation and rapid titration of foundational medical therapy after hospital discharge for decompensated HF to reduce the risk of HF rehospitalization or death.	STRONG	MODERATE

HF: heart failure; POCUS: point-of-care ultrasound.

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7.18. Special Conditions in Decompensated Heart Failure

7.18.1. Takotsubo Syndrome

Takotsubo syndrome (TTS) may present as DHF with acute pulmonary edema (8%) or CS (7%–10%). The diagnosis is based on a history of a preceding physical or emotional trigger in postmenopausal women, with the presence of new regional wall motion abnormalities on echocardiography in the absence of obstructive CAD, followed by improvement or complete recovery of ventricular function within a short period.^{539,540}

The main differential diagnoses are ST-segment elevation myocardial infarction (STEMI) and acute myocarditis, given their similar clinical presentation, ECG findings, echocardiographic abnormalities, and biomarker profiles. The absence of obstructive CAD on CCTA or invasive coronary angiography and an elevated NT-proBNP-to-troponin ratio strongly support the exclusion of acute myocardial infarction, whereas abnormal CMR results and the progressive resolution of regional wall motion abnormalities on echocardiography are key features supporting the exclusion of acute myocarditis (Chart 7.8).

Management of DHF in patients with TTS should follow current guideline recommendations and includes

Chart 7.8 – Clinical characteristics and findings from noninvasive diagnostic modalities in Takotsubo syndrome, acute myocardial infarction, and acute myocarditis^{80,541-544}

	Takotsubo syndrome	AMI	Myocarditis
Clinical presentation	Precordial pain, dyspnea postmenopausal women, trigger	Precordial pain, middle-aged men	Precordial pain, male adolescents or young adults
ECG	ST-segment elevation, T-wave inversion, LBBB, prolonged Qtc interval	ST-segment elevation or depression, LBBB	Nonspecific ST-segment abnormalities
Echocardiography	Regional wall-motion abnormalities with anterior or apical akinesia (“apical ballooning”) and basal hypercontractility; rapid recovery of ventricular function and wall-motion abnormalities	Regional akinesia or hypokinesia; persistent wall-motion abnormalities with little to no early improvement in ventricular function	Diffuse hypokinesia or regional wall-motion abnormalities; regional myocardial wall thickening due to myocardial edema; no early recovery of ventricular function or wall-motion abnormalities; may be associated with pericardial effusion
Biomarkers	Marked elevation of NT-proBNP with a high NT-proBNP/troponin T ratio	Marked elevation of troponin with a lower NT-proBNP/troponin T ratio	Elevated troponin with a pattern similar to or more sustained than that of AMI
CMR	Regional ballooning involving the anterior or apical segments; possible RV involvement; LGE uncommon; myocardial edema on T2 mapping corresponding to the region of wall-motion abnormality	Endocardial or transmural LGE corresponding to the region of wall-motion abnormality	Positive Lake Louise criteria
Coronary angiography	Absence of obstructive CAD in the region of wall-motion abnormality	Presence of obstructive CAD in the region of wall-motion abnormality	Absence of obstructive CAD in the region of wall-motion abnormality

CAD: coronary artery disease; CMR: cardiac magnetic resonance imaging; ECG: electrocardiogram; LBBB: left bundle branch block; LGE: late gadolinium enhancement; NT-proBNP: N-terminal pro-B-type natriuretic peptide; Qtc, heart rate-corrected QT interval.

Table 7.16 – Recommendations for the diagnostic evaluation of patients with decompensated heart failure and suspected myocarditis^{69,543,559}

Recommendation	Strength of recommendation	Certainty of evidence
We recommend IN FAVOR OF cardiac magnetic resonance imaging using the 2018 Lake Louise criteria.	STRONG	MODERATE

In patients with new-onset DHF at high risk whose clinical presentation resembles myocardial infarction with or without ST-segment elevation, we recommend IN FAVOR OF invasive coronary angiography to establish the differential diagnosis.

STRONG

HIGH

Table 7.17 – Recommendations for endomyocardial biopsy in patients with suspected myocarditis and decompensated heart failure^{555,557,558}

Recommendation	Strength of recommendation	Certainty of evidence
In patients with new-onset DHF (<2 weeks) of unknown cause that is unresponsive to standard therapy, with or without hemodynamic deterioration, we recommend IN FAVOR OF performing EMB.	STRONG	MODERATE
In patients with high clinical suspicion of severe lymphocytic myocarditis, giant cell myocarditis, or necrotizing eosinophilic myocarditis, we recommend IN FAVOR OF performing EMB.	STRONG	MODERATE

HF: heart failure; EMB: endomyocardial biopsy.

ventilatory support, diuretics, ACEIs, ARBs, sacubitril-valsartan, beta-blockers, MRAs, and SGLT2 inhibitors as clinically indicated. ACEIs have been associated with improved 1-year survival and reduced risk of recurrence. In contrast, beta-blockers have not demonstrated improvements in survival or recurrence rates at 30 days or 1 year post-discharge, although a reduction in 1-year mortality has been observed in the subgroup of patients with hypertension.⁵⁴⁵⁻⁵⁴⁷

CS develops in 6% to 20% of patients within the first 72 hours of hospital admission. The initial therapeutic consideration is to determine whether hypotension results from diffuse LV systolic dysfunction or from LV outflow tract obstruction (LVOTO), which occurs in 20% to 25% of patients. In patients with LVOTO, vasoactive agents, inodilators, vasodilators, diuretics, and the intra-aortic balloon pump (IABP) should be avoided because they may exacerbate the obstruction. Recommended treatment consists of volume expansion and administration of a short-acting intravenous selective beta-blocker, such as esmolol.⁵⁴⁸

When CS results primarily from ventricular dysfunction rather than LVOTO, vasoactive agents such as norepinephrine are commonly used in clinical practice. However, they should be avoided whenever possible or administered at the lowest effective doses because of their potential to exacerbate myocardial injury, worsen ventricular dysfunction, and prolong the duration of shock.⁵⁴⁹⁻⁵⁵¹

In the absence of LVOTO, levosimendan or milrinone might be considered as alternatives to vasoactive agents because they do not activate neuro-adrenergic receptors and have been associated with improvements in clinical/hemodynamic status and ventricular function. In patients with CS refractory to pharmacologic therapy, MCS should be considered, including IABP, ECMO, or Impella, in accordance with current guideline recommendations. IABP is contraindicated in patients with LVOTO.⁵⁵²⁻⁵⁵⁴

7.18.2. Myocarditis

Acute myocarditis may present as DHF in approximately 26% of patients, with clinical manifestations ranging from mild HF to fulminant myocarditis.⁵⁵⁵ At hospital admission, the differential diagnosis most commonly includes myocardial infarction and TTS because of their similar clinical presentation and findings on complementary diagnostic tests. CMR, invasive coronary angiography, and EMB are the cornerstone diagnostic modalities for confirming acute myocarditis in patients presenting with DHF.^{541,542} Management of HF and ventricular dysfunction in myocarditis should follow current HF guidelines and includes ACEIs or ARBs, sacubitril-valsartan, beta-blockers, MRAs, and SGLT2 inhibitors.

Fulminant myocarditis typically presents as new-onset DHF with symptom duration of < 2 weeks, accompanied by hemodynamic instability and severe ventricular dysfunction. These patients may rapidly progress to CS, requiring inotropic support and/or MCS.⁵⁵⁶ The most common etiologies identified by EMB include lymphocytic, viral, giant cell, and eosinophilic myocarditis. At admission, the differential diagnoses are myocardial infarction and TTS because of overlapping clinical and diagnostic features. EMB should be performed as soon as the patient's clinical condition permits to establish the diagnosis of myocarditis, identify the underlying etiology, and guide disease-specific therapy with potential prognostic benefit, as demonstrated in clinical registries.^{557,558}

Tables 7.16 and 7.17 summarize the recommendations for the diagnostic workup of suspected myocarditis in patients presenting with DHF. Initial management should focus on clinical/hemodynamic stabilization of CS using inotropic and vasopressor support, combined with MCS, in accordance with current guideline recommendations for the management of CS.^{556,560}

Table 7.18 summarizes the recommendations for the treatment of fulminant myocarditis in patients with DHF

Table 7.18 – Recommendations for the treatment of fulminant myocarditis in patients with decompensated heart failure^{541,561-567}

Recommendation	Strength of recommendation	Certainty of evidence
In patients with left ventricular systolic dysfunction, whether symptomatic or asymptomatic, we recommend IN FAVOR OF treatment with prognosis-modifying therapies according to current HF guidelines.	STRONG	MODERATE
In patients with EMB-confirmed giant cell myocarditis, autoimmune myocarditis, cardiac sarcoidosis, lymphocytic myocarditis, or eosinophilic myocarditis associated with ventricular dysfunction, we recommend IN FAVOR OF immunosuppressive therapy.	STRONG	MODERATE
In patients with EMB-confirmed myocarditis, negative viral PCR, and severe ventricular dysfunction, we recommend IN FAVOR OF immunosuppressive therapy.	STRONG	MODERATE
In patients with fulminant myocarditis, we recommend IN FAVOR OF treatment with inotropic support and short-term mechanical circulatory support.	STRONG	MODERATE
In patients with suspected myocarditis without confirmation by EMB, we recommend AGAINST immunosuppressive therapy.	STRONG	MODERATE

HF: heart failure; EMB: endomyocardial biopsy; PCR: polymerase chain reaction.

8. Advanced Heart Failure

8.1. Definition, Epidemiology, and Prognosis

HF is a progressive condition characterized by variable periods of symptomatic stability that are frequently interrupted by episodes of clinical deterioration.^{568,569} These episodes have been recognized as distinct phases in the trajectory of HF and are associated with a substantially worse prognosis. Early identification of these patients is essential to enable timely referral to specialized centers, particularly given the increasing complexity of care and the need for multidisciplinary evaluation to determine the most appropriate therapeutic strategy.⁵⁷⁰

8.1.1. The Concept of Worsening Heart Failure (Transition to Stage D)

Worsening HF represents a phase characterized by clinical deterioration in patients with a previous diagnosis of HF who are receiving optimal therapy (Figure 8.1).⁵⁶⁸ Although traditionally associated with acute decompensation requiring hospitalization, worsening HF is now also recognized in the outpatient setting, particularly when intensification of therapy is required, most commonly with an increased need of diuretics.⁵⁷¹

Worsening HF may be triggered by several factors, including poor treatment adherence, infections, and arrhythmias, among other conditions. This diversity of triggers underscores the importance of patient-centered care and individualized risk assessment.²³ Recently, several cardiology societies have recognized and incorporated the concept of worsening HF as an important marker of clinical transition between stages C and D of HF, reflecting the progressive and degenerative nature of the disease. Although the current definition of worsening HF still lacks more precise standardization, particularly for outpatients, early recognition of worsening episodes is essential to prevent hospitalization, reduce morbidity and mortality, and enable structured management. Nevertheless, early

identification of worsening HF remains underrecognized in both clinical trials and routine clinical practice.

A diagnosis of HF carries a substantial intrinsic clinical risk (baseline risk), which can be reduced through the implementation of GDMT. Even during periods of clinical stability, patients continue to face a residual risk of clinical deterioration, which may lead to recurrent hospitalizations and new cardiovascular events, characterizing worsening HF.

As shown in Figure 8.1, patients in the worsening phase may respond to optimized therapy and return to a state of residual risk or progress to the advanced-risk stage (arrows).

8.1.2. Definition of Advanced Heart Failure (Stage D)

The terms advanced HF, refractory HF, end-stage HF, and stage D HF are commonly used to describe patients with persistent symptoms and severe functional limitation despite optimal pharmacologic and nonpharmacologic therapy.^{572,573} These patients should be considered for evaluation at specialized centers to determine eligibility for advanced therapeutic strategies, including heart transplant, MCS, and palliative care.⁵⁷⁴

Because no single criterion defines stage D HF, its diagnosis requires recognition of a constellation of clinical, hemodynamic, and functional features, including worsening symptoms, hospitalizations or unplanned health care visits, and evidence of progressive ventricular dysfunction despite optimal therapy. Risk stratification may be further refined using systems such as the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles, which assist in prioritizing patients and selecting appropriate advanced therapies (Figure 8.2).⁵⁷⁵⁻⁵⁷⁷ The INTERMACS profiles are summarized in Chart 8.1.

8.1.3. INTERMACS Profiles

The INTERMACS profiles were developed to identify patients who may be candidates for durable MCS.⁵⁷⁷

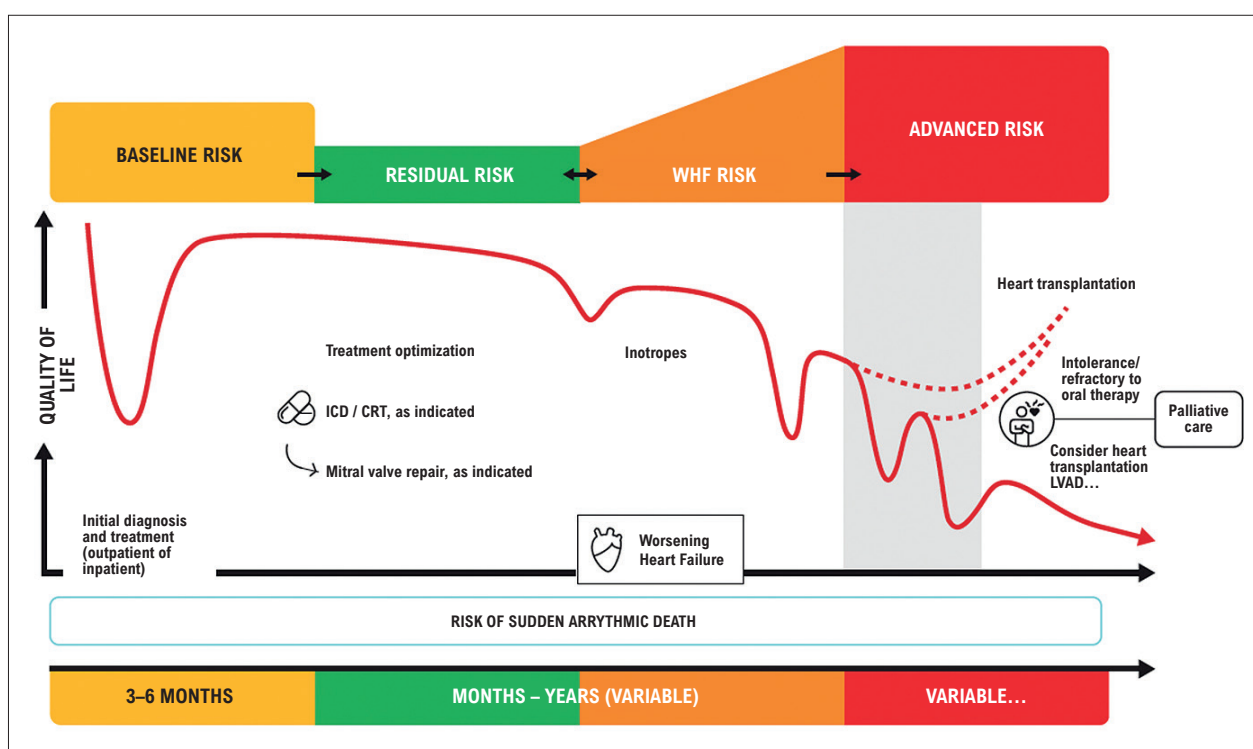


Figure 8.1 – Journey and risk profiles of patients with heart failure. ICD: implantable cardioverter-defibrillator; HF: heart failure; CRT: cardiac resynchronization therapy. Adapted from Greene et al.⁵⁶⁸

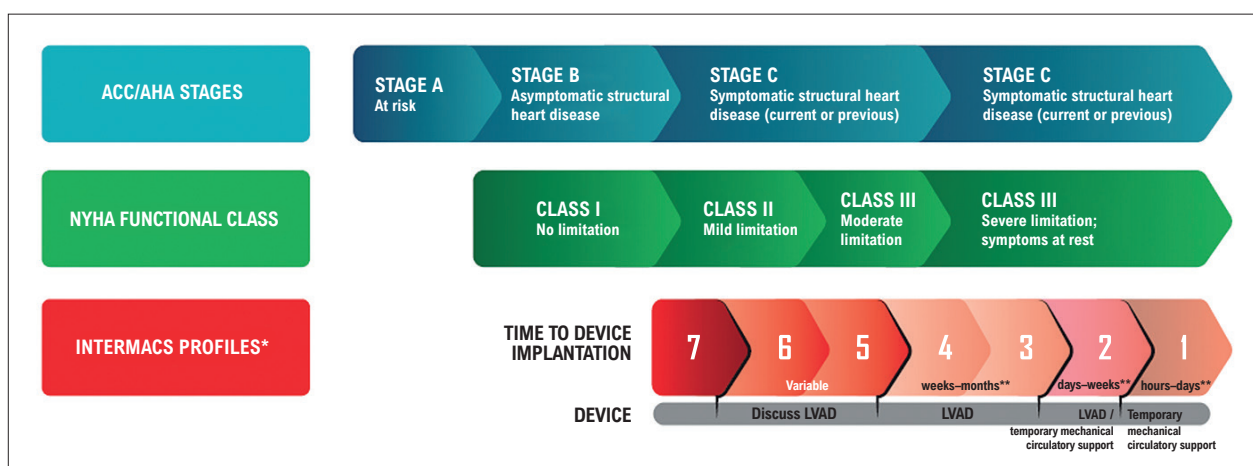


Figure 8.2 – Prognostic classification systems in heart failure. Staging described by the American College of Cardiology (ACC), functional classification of the New York Heart Association (NYHA), and profiles of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS). VAD: ventricular assist device; HF: heart failure. Adapted from Tiruby VAD: ventricular assist device; HF: heart failure. Adapted from Truby et al.⁵⁷⁶

Based on clinical descriptors, these profiles also serve as prognostic indicators for patients with HF being considered for heart transplant or implantation of MCS devices (Chart 8.1).^{578,579} Use of the INTERMACS classification influences both candidate selection and the timing of MCS device implantation, particularly among hospitalized patients. However, data supporting the utility of this tool in the

outpatient setting (INTERMACS profiles 4–7), remain limited and warrant further investigation.

A recent study, the REVIVAL Registry,⁵⁸⁰ evaluated 400 outpatients and demonstrated that a lower INTERMACS profile was associated with greater functional limitation and an increased risk of death, hospitalization, durable MCS, and heart transplant at 1 year. These findings indicate that INTERMACS

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Chart 8.1 – Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles

Profile	Description	Hemodynamic status	Time to intervention
I	Critical cardiogenic shock	Persistent hypotension despite treatment with inotropic agents and IABP, associated with end-organ dysfunction	Hours
II	Progressive decline despite inotropic therapy	Progressive deterioration of renal and hepatic function, nutritional depletion, and lactatemia despite optimal inotropic therapy	Days
III	Stable but inotrope dependent	Clinical stability while receiving continuous inotropic therapy, but with a history of unsuccessful attempts at weaning	Weeks to months
IV	Frequent hospitalizations	Persistent fluid retention, symptoms at rest, and recurrent emergency department visits	Weeks to months
V	Housebound, exertion intolerant	Severely limited tolerance to activity but comfortable at rest despite persistent fluid retention	Variable urgency, depending on nutritional status and the degree of end-organ dysfunction
VI	Exertion limited	Moderately limited tolerance to exertion and no signs of hypervolemia	Variable urgency, depending on nutritional status and the degree of end-organ dysfunction
VII	NYHA class III	Hemodynamic stability without evidence of hypervolemia	No indication

IABP: intra-aortic balloon pump; NYHA: New York Heart Association.

profiling provides relevant prognostic information and may assist in triaging outpatients to advanced HF therapies.

8.1.4. Red Flags – The I NEED HELP Mnemonic

Referral of patients with HF to a specialist is essential to optimize ongoing clinical management and assess the need for advanced HF therapies.⁵⁸¹ Delayed referral may increase the risk of RV failure, renal and hepatic dysfunction, pulmonary hypertension, and cardiac cachexia, resulting in poorer outcomes after advanced HF therapies or even rendering patients ineligible for certain interventions because of excessive disease severity, such as heart transplant or implantation of a durable MCS device.⁵⁸²

Determining the optimal timing for referral, however, may be challenging because prognostic assessment in HF is complex.⁵⁸³ One tool developed to facilitate this decision is the I NEED HELP mnemonic. It incorporates several risk factors that have been consistently associated with increased mortality in patients with HF and may help identify individuals who should be referred for potentially life-saving therapies that are not available in primary care settings (Chart 8.2).⁵⁸⁴ A recent multicenter cohort study including 1149 patients with HF demonstrated that the risk of all-cause mortality or HF hospitalization increases with the increasing number of I NEED HELP criteria present.^{584,585}

8.1.5. Invasive Hemodynamic Assessment

Once the diagnosis of advanced HF has been established, selection of the most appropriate therapeutic strategy

depends on the patient's hemodynamic status. Measurements obtained using a pulmonary artery catheter may play a pivotal role in this process. Chart 8.3 summarizes the key invasive hemodynamic parameters and their corresponding clinical interpretation.

8.1.6. The Role of the Advanced Heart Failure Specialist

The role of the advanced HF specialist has yet to achieve broader formal and informal recognition among cardiology societies and the cardiology community.^{586,587} However, the complexity of patients with advanced HF and the contemporary management of this condition have made interdisciplinary collaboration increasingly important both within and beyond cardiology, with the advanced HF specialist playing a critical role across several domains.^{588,589} First, in collaboration with the general cardiologist, the advanced HF specialist helps identify red flags suggestive of advanced disease, thereby avoiding missed opportunities for timely intervention, particularly when advanced therapies are complex and time sensitive. In addition, decisions regarding advanced treatment options, such as heart transplant, implantation of short-term or durable MCS devices, and even palliative care, should involve an advanced HF specialist working in conjunction with a multidisciplinary team and, ideally, surgeons experienced in these procedures. The role of the advanced HF specialist has also become increasingly important in the management of CS, serving as a key member of the shock team, in which specialists from multiple disciplines collaborate to make rapid decisions that may substantially influence clinical outcomes.⁵⁹⁰⁻⁵⁹²

Chart 8.2 – The I NEED HELP mnemonic: red flags in patients with heart failure

I	Inotrope dependence
N	NYHA class III/IV (persistent)
E	End-organ dysfunction
E	Ejection fraction < 20%
D	Defibrillator shocks (recurrent appropriate shocks)
H	Hospitalizations and emergency department visits in the last 12 months (recurrent)
E	Edema despite escalating diuretics (persistent)
L	Low systolic blood pressure < 90 mm Hg (persistent)
P	Progressive intolerance or down-titration of guideline-directed medical therapy

NYHA: New York Heart Association.

Chart 8.3 – Parameters for invasive hemodynamic monitoring

Parameter	Abbreviation	Value	Unit	Parameter	Abbreviation	Value	Unit
Mean arterial pressure	MAP	70–105	mmHg	Diastolic pulmonary gradient	DPG	≤ 5	mmHg
Central venous pressure	CVP	2–8	mmHg	Systemic vascular resistance	SVR	800–1200	dyn·s·cm ⁻⁵
Cardiac output	CO	4–8	L/min	Pulmonary vascular resistance	PVR	100–250	dyn·s·cm ⁻⁵
Cardiac index	CI	2.5–4.0	L/min/m ²	Pulmonary artery pulsatility index	PAPi	> 1.5	
Pulmonary capillary wedge pressure	PCWP	6–12	mmHg	Right ventricular stroke work index	RVSWI	5–10	g·m/m ²
Pulmonary artery systolic pressure	PASP	15–30	mmHg	Left ventricular stroke work index	LVSWI	50–62	g·m/m ²
Pulmonary artery diastolic pressure	PADP	4–12	mmHg	Cardiac power output	CPO	> 0.8 (low < 0.6)	W

Finally, the advanced HF specialist contributes to the rational allocation of technological and financial resources, which are often non-negligible in the management of advanced HF. Appropriate use of these resources is frequently essential to improve both survival and quality of life in this patient population.

8.2. Clinical Management

8.2.1. Management of Prognosis-Modifying Pharmacologic Therapy

Despite the growing number of patients who progress to advanced HF, this population has traditionally been underrepresented in clinical trials evaluating the benefits of pharmacologic therapies. The proportion of patients with NYHA class IV HF in trials of sacubitril-valsartan and SGLT2

inhibitors, such as PARADIGM-HF, EMPEROR-REDUCED, and DAPA-HF, was < 1%.^{140,146,147} Only a limited number of trials have exclusively enrolled patients with NYHA class III or IV or worsening HF, and most of them were published more than 20 years ago.⁵⁹³ The most recent RCT evaluating pharmacologic therapy in the setting of advanced HF was the LIFE trial, which compared sacubitril-valsartan with valsartan alone in outpatients. After being terminated early during the COVID-19 pandemic, the trial failed to demonstrate a benefit of sacubitril-valsartan over valsartan in reducing the primary outcome of NT-proBNP levels.⁵⁹⁴ For SGLT2 inhibitors, the studies that most closely reflect the advanced HF population are the SOLOIST-WHF and EMPULSE trials, both of which enrolled patients with worsening HF and demonstrated reductions in mortality and/or HF events.^{148,154} Although conducted earlier, the COPERNICUS and RALES trials established the role of beta-blockers and MRAs, respectively, in patients with NYHA class IV HF.^{127,136}

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Table 8.1 – Recommendations for the use of prognosis-modifying pharmacologic therapy in advanced heart failure

Recommendation	Strength of recommendation	Certainty of evidence
In patients with advanced HF, in the absence of contraindications, we recommend IN FAVOR OF prescribing the 4 pillars at the maximum tolerated doses.	STRONG	MODERATE
In patients with advanced HF, we recommend IN FAVOR OF slower up-titration of pharmacologic therapy.	STRONG	MODERATE
In patients with advanced HF, we recommend IN FAVOR OF careful monitoring for adverse effects, including hypotension, electrolyte disturbances, and deterioration of renal function.	STRONG	MODERATE

HF: heart failure.

A more gradual approach to treatment optimization, involving sequential introduction of pharmacologic classes and slower up-titration, may be beneficial in patients with advanced HF. This strategy was evaluated for RAAS inhibitors in an RCT comparing ACEI/ARB up-titration over 6 weeks vs. 3 weeks. Patients assigned to the slower up-titration strategy achieved higher target doses and maintained them for a longer duration.⁵⁹⁵ Furthermore, as observed in the LIFE trial, patients with advanced HF may be at increased risk of treatment-related adverse events.⁵⁹⁴ Therefore, careful monitoring for medication-related side effects is recommended.

Table 8.1 summarizes the recommendations for the use of prognosis-modifying pharmacologic therapy in advanced HF.

8.2.2. Management of Refractory Congestion

Refractory congestion is common among patients with advanced HF, particularly those with a restrictive phenotype, and its clinical management remains challenging. In general, the therapeutic strategies described previously, including continuous intravenous diuretic infusion, combination therapy with different classes of diuretics, hypertonic saline, acetazolamide, and/or UF, may be used in combination to achieve effective decongestion in patients with refractory disease. A detailed discussion of these approaches is provided in Section 7.5.

8.2.3. Congestion Monitoring (Telemonitoring Devices)

Congestion is a well-established prognostic marker in HF. In this context, strategies aimed at monitoring and early detection of congestion may improve clinical outcomes, particularly by reducing hospitalizations, thereby helping to prevent progression to advanced HF and facilitating the management of these patients. Various monitoring approaches have been used and investigated, ranging from simple methods, such as weight telemonitoring, to implantable hemodynamic monitoring devices, and, more recently, noninvasive multiparameter monitoring systems.⁵⁹⁶

Early studies of telemonitoring based on structured support and telephone transmission of body weight, vital signs, and symptoms yielded promising initial results.^{597,598} However, these findings were not confirmed in larger randomized trials. A meta-analysis including

10,981 patients from 29 telemonitoring studies in HF demonstrated a modest benefit in reducing hospitalizations and improving quality of life.³⁹¹

Although HF symptoms often appear to worsen abruptly, cardiac filling pressures typically increase gradually over 3 to 4 weeks before hospitalization.⁵⁹⁹ Based on this rationale, the CHAMPION trial demonstrated that an implantable PAP monitor (CardioMEMS) reduced HF hospitalizations.⁶⁰⁰⁻⁶⁰² The subsequent GUIDE-HF trial, which enrolled nearly twice as many patients as CHAMPION, evaluated the composite outcome of death and HF events during periods both before and during the COVID-19 pandemic. Although the overall analysis did not demonstrate a significant reduction in HF events, prespecified analyses of the pre-pandemic period suggested a clinical benefit.⁶⁰² A more recent meta-analysis including CHAMPION, GUIDE-HF, and the unpublished LAPTOP-HF trial reinforced these findings, demonstrating a 36% reduction in HF hospitalizations ($p < 0.001$) and a modest 25% reduction in mortality ($p = 0.043$).⁶⁰³ Despite the potential benefit, the invasive nature and high cost of implantable hemodynamic monitors currently limit their widespread use in our setting.

In addition to implantable devices, noninvasive monitoring strategies have also been investigated. These include intrathoracic impedance monitoring using implantable electronic devices, which correlates with PCWP and may facilitate earlier detection of volume overload,^{596,604} as well as wearable technologies such as remote dielectric sensing (ReDS), which estimates intrathoracic fluid status and thereby provides an indirect assessment of congestion.^{596,605} Despite a sound pathophysiological rationale, RCTs evaluating these approaches have yielded only modest results.

More recently, noninvasive multiparameter remote monitoring systems that integrate multiple digital biomarkers have been developed to enable the detection of subclinical HF decompensation.⁶⁰⁶ Rather than relying on a single physiological parameter, these technologies analyze multiple biomarkers of congestion using sophisticated algorithms, generating actionable data that may facilitate timely clinical intervention. Several devices and platforms are currently under evaluation or have been incorporated into clinical practice, including some that have received U.S. Food and Drug Administration (FDA) approval for

Table 8.2 – Recommendations for telemonitoring in patients with advanced heart failure

Recommendation	Strength of recommendation	Certainty of evidence
In patients with advanced heart failure, we recommend IN FAVOR OF telemonitoring as a strategy to reduce hospitalizations.	STRONG	LOW

commercial use.⁶⁰⁷ Despite these advances, however, the clinical utility of noninvasive multiparameter remote monitoring remains uncertain, and additional studies are needed to establish its efficacy and safety before its routine implementation in clinical practice. Table 8.2 summarizes the recommendations for telemonitoring in patients with advanced HF.

8.3. Mechanical Circulatory Support

8.3.1. Indications and Therapeutic Strategies

CS is associated with high rates of morbidity and mortality. In this condition, the heart is unable to maintain adequate circulation, resulting in insufficient tissue perfusion and multiple organ failure.

Short-term MCS plays a key role in the management of severe or refractory CS, providing hemodynamic support to maintain end-organ perfusion for periods ranging from hours to weeks or even months. These devices may be used as a bridge to recovery, a bridge to decision, or to facilitate definitive therapies such as heart transplant or implantation of a durable ventricular assist device.⁶⁰⁸

Bridge to recovery: This strategy is appropriate when recovery of ventricular function is anticipated following an acute insult. In such cases, the device can be removed once ventricular function has recovered (eg, in post-acute myocardial infarction ventricular dysfunction, TTS, and myocarditis).

Bridge to decision: This strategy should be considered in critically ill patients who require immediate hemodynamic support because of the imminent risk of death from cardiac failure. In this setting, several clinical scenarios may evolve (lack of neurological recovery, multiple organ dysfunction, and hemodynamic stabilization requiring additional MCS, among others), making it impossible to determine the definitive treatment strategy at the time of device implantation (eg, after cardiac arrest).

Bridge to candidacy: This strategy applies to patients who have temporary contraindications to heart transplant (pulmonary hypertension, malignancy, obesity), but who may become eligible once these conditions have been successfully addressed.

Bridge to transplant: This strategy should be considered in patients with progressive clinical deterioration who are eligible for heart transplant but are unlikely to receive a donor organ promptly. In this setting, the device can provide sustained hemodynamic support and clinical stabilization until transplant becomes available.

8.3.2. Short-Term Mechanical Circulatory Support

8.3.2.1. Types of Devices

Short-term MCS devices are external systems implanted either percutaneously or through surgical implantation. They are characterized by rapid deployment and lower procedural invasiveness, with intended use typically limited to days or a few weeks. Device selection should be guided by the degree of hemodynamic support required, the etiology and phenotype of CS, the anticipated duration of support, and institutional experience with the device. Available options include IABP, LVAD and RVAD (Impella, TandemHeart, and CentriMag), and ECMO.

Two percutaneous devices are specifically designed for isolated RV support (Impella RP and ProtekDuo), although neither is currently available in our setting. In patients with biventricular failure and/or concomitant respiratory failure, ECMO is the most commonly used support modality. In addition, temporary support devices (IABP and Impella) may be combined with ECMO to achieve LV unloading in patients with elevated PCWP and LV distension while receiving ECMO support.⁴²²

- **IABP:** Although IABP remains the most widely used MCS device in CS, the IABP-SHOCK and IABP-SHOCK II trials demonstrated no mortality benefit in patients with CS.⁶⁰⁹ However, some evidence suggests that IABP may be beneficial in patients with DHE.⁶¹⁰
- **Impella:** The Impella device is an option for the treatment of CS because it increases cardiac output while unloading the LV, reducing LV end-diastolic pressure. Several models are available (Impella 2.5, Impella CP, Impella 5.0, and Impella 5.5), each providing progressively greater flow capacity. Recently, the DanGer Shock trial demonstrated a reduction in mortality among patients with post-acute myocardial infarction CS treated with Impella.⁵¹⁴
- **TandemHeart:** The TandemHeart device provides greater hemodynamic support than the IABP and some Impella models. However, evidence supporting its use in high-risk patients remains limited.⁶¹¹
- **Extracorporeal life support (ECLS/ECMO):** ECMO has been increasingly adopted as a first-line temporary support strategy, particularly in patients with biventricular failure and/or concomitant respiratory failure.⁶¹² A randomized trial comparing ECMO with standard medical therapy in patients with rapidly deteriorating clinical status or CS found no difference in 30-day mortality.⁶¹³ An analysis of the Extracorporeal Life

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Support Organization (ELSO) registry involving 2987 patients receiving VA-ECMO for decompensated chronic HF showed that LV unloading, performed in 31.5% of patients, was associated with improved outcomes, including lower mortality.⁶¹⁴ The combination of ECMO with IABP or Impella (ECPELLA) has attracted increasing interest because of its potential to reduce mortality, although at the expense of higher complication rates.⁶¹⁵ Observational studies have suggested that ECMO support lasting more than 7 days is associated with worse prognosis and increased mortality when used as a bridge to durable MCS.⁶¹⁶

- Continuous-flow centrifugal pump (CentriMag®): CentriMag® is a magnetically levitated centrifugal pump designed to minimize blood trauma. Although it requires surgical implantation through a median sternotomy or a minimally invasive approach, it provides highly versatile circulatory support for up to 30 days, exceeding the typical duration of other short-term support devices. The system may be used for isolated RV support, isolated LV support, or biventricular support. Available evidence is limited to small case series.^{616,617}
- Berlin Heart EXCOR®: The Berlin Heart EXCOR® is an extracorporeal pulsatile ventricular assist device with greater durability, allowing its use as either short-term or prolonged MCS in patients with CS. It can be configured for univentricular or biventricular support; however, published studies have reported high rates of thrombotic complications.⁶¹⁸

8.3.2.2. Indications in Advanced Heart Failure

Although RCTs have been conducted almost exclusively in patients with CS related to acute myocardial infarction or refractory cardiac arrest, the optimal timing, appropriate patient selection, and choice of MCS device are based primarily on observational evidence and expert consensus, especially in nonischemic CS.

In patients with advanced (stage D) HF, characterized by reduced LVEF and classified as SCAI shock stages C or E, who develop progressive hemodynamic deterioration despite inotropic support, implantation of a short-term MCS device should be considered.⁵¹⁸ The primary goal of mechanical support is to reduce cardiac preload and afterload while increasing cardiac output, thereby restoring adequate end-organ perfusion.

Indicators of severe CS in this population include a persistently low cardiac index (< 2.2 L/min/m²), CPO < 0.6 W, SBP < 90 mm Hg, serum lactate > 2 mmol/L, and evidence of RV failure, as indicated by either a CVP-to-PCWP ratio (CVP/PCWP) > 0.86 or a PAPI ≤ 0.9 .⁶¹⁹

Unlike patients with DHF, those with chronic HF have adapted to a sustained low-output state through chronic neurohormonal activation, allowing greater tolerance of congestion and impaired tissue perfusion.⁶¹⁹ Therefore, in some cases, even modest improvements in cardiac output may provide temporary hemodynamic stabilization with relatively limited invasiveness, facilitating subsequent treatment decision-making.⁶²⁰

Because of its widespread availability, low cost, and minimally invasive nature, IABP should be considered as an initial support strategy in patients with chronic HF. Although dedicated studies remain limited, observational cohort studies have reported favorable outcomes when the IABP is used as a bridge to more definitive therapies. Huang et al. followed 218 patients with chronic HF who received IABP for CS. The mean (SD) cardiac output increase was 0.57 (0.85) L/min, and mean PAP (mPAP) reduction was 5.1 (7.6) mmHg. Fifty-six patients (25.7%) were identified as IABP responders, with a mean (SD) cardiac output increase of 1.21 (0.87) L/min and mPAP reduction of 12.1 (5.9) mmHg. Patients with SVR > 1300 dyn-s/cm-5, moderate-to-severe MR, and PAPI > 2 were more likely to respond favorably to IABP support.⁶²¹

Hemodynamic parameters derived from pulmonary artery catheterization, such as CPO and PAPI, may not only guide the indication for implantation but also identify potential responders to temporary support. Studies have shown that CPO < 0.54 W is correlated with a worse prognosis and the need for heart transplant or durable MCS.⁶²²

The Impella 5.5 system (currently unavailable in our setting) has demonstrated favorable safety outcomes when used as a bridge to transplant. Compared with the IABP, it provides greater cardiac output, and its placement via right axillary artery allows rehabilitation while awaiting transplantation.⁶²³

Table 8.3 summarizes the recommendations for the use of short-term MCS in patients with advanced HF

8.3.2.3. Complications

Contraindications and complications (Chart 8.4) may be classified as either general, applicable to all devices, or

Table 8.3 – Recommendations for the use of short-term mechanical circulatory support in patients with advanced heart failure

Recommendation	Strength of recommendation	Certainty of evidence
In patients with advanced HF, we recommend IN FAVOR OF implantation of an intra-aortic balloon pump in the setting of clinical deterioration despite inotropic therapy.	STRONG	LOW
In patients with advanced HF, we recommend IN FAVOR OF extracorporeal membrane oxygenation in patients with INTERMACS profiles 1 or 2 as a bridge to heart transplant or other mechanical circulatory support devices.	STRONG	MODERATE

HF: heart failure.

Chart 8.4 – Comparison of temporary mechanical circulatory support devices

Device	IABP	Impella CP / 5.0	TandemHeart	ECMO	CentriMag	EXCOR
Device mechanism	Pneumatic Pulsatile	Axial continuous flow	Centrifugal	Centrifugal	Centrifugal	Pulsatile
Insertion cannula – drainage – return	7–9 Fr	14/21 Fr	21 Fr 17 Fr	21–25 Fr 15–20 Fr	24–32 Fr 15–22 Fr	27–48 36–48
Hemodynamic support	0,5 L/min	2-5 L/min	4 L/min	> 4 L/min	5-7 L/min	8 L/min

IABP: intra-aortic balloon pump; ECMO: extracorporeal membrane oxygenation.

device-specific. Absolute contraindications include severe sepsis, brain injury, multiple organ failure, and advanced or metastatic malignancy with no reasonable prognosis.

Relative contraindications should be evaluated by a multidisciplinary team and include coagulopathy or inability to receive anticoagulation, limited or difficult vascular access, severe atherosclerosis, advanced liver disease, and advanced age

8.3.3. Durable Mechanical Circulatory Support

8.3.3.1. Types of Devices

Durable MCS devices have undergone substantial technological advances, particularly with respect to their propulsion systems and flow characteristics. Progressive miniaturization has improved device efficiency while reducing complication rates, especially those related to hemocompatibility, including non-surgical bleeding, neurological events, and thromboembolic complications arising from blood-device interactions. The device currently available for clinical use is a third-generation, continuous-flow centrifugal LVAD with a fully magnetically levitated impeller.

8.3.3.2. Survival

The third-generation durable MCS device was evaluated in the MOMENTUM 3 trial, which demonstrated a significant reduction in hemocompatibility-related morbidity and mortality, as well as less frequent need for pump replacement.^{624,625} In the initial 2-year analysis, the third-generation device significantly reduced the primary composite endpoint of survival free of disabling stroke or pump replacement due to pump thrombosis.^{624,625}

The 5-year follow-up demonstrated superior overall survival with the third-generation durable MCS device compared with the second-generation device.⁶²⁶ Five-year survival was 58.4% with the third-generation device versus 43.7% with the second-generation device.⁶²⁶

The 2025 INTERMACS report, covering the period from 2014 to 2024, demonstrated that, even in real-world clinical practice, the third-generation durable MCS device has achieved excellent long-term survival. Reported outcomes showed significantly higher survival with fully magnetically

levitated devices than with non-magnetically levitated devices at both 1 year (85.7% vs. 78.4%) and 5 years (59.7% vs. 43.7%).⁶²⁷

8.3.3.3. Complications

The operation of durable MCS devices continues to depend on external batteries, and one of the most common device-related complications is driveline exit-site infection, involving the percutaneous cable that provides power and data communication to the pump. Over a 5-year period, approximately 5% to 20% of patients develop a driveline exit-site infection.⁶²⁷ In addition, approximately 11% of patients experience wound colonization requiring infection-control measures.

Hemocompatibility-related complications have markedly declined after the introduction of the third-generation magnetically levitated durable MCS device, as discussed previously. This improvement has prompted studies evaluating the possibility of reducing the anticoagulation/antiplatelet regimen. In 2023, the ARIES-HM3 trial demonstrated that warfarin monotherapy, without concomitant antiplatelet therapy, was safe and did not increase the risk of thrombotic events.⁶²⁸ Based on these findings, the current recommendation for patients receiving a third-generation durable MCS device is warfarin alone. Discontinuation of routine antiplatelet therapy has also been associated with a reduction in gastrointestinal bleeding.

Table 8.4 summarizes the recommendations for the use of durable MCS

8.4. Heart Transplant

Despite the advances in the pharmacologic and nonpharmacologic treatment of HF over recent decades, with substantial reductions in all-cause mortality, cardiovascular mortality, and morbidity, including recurrent hospitalizations, a considerable proportion of patients continue to progress to advanced HF that is refractory to conventional therapies. In this setting, heart transplant remains the treatment of choice.

A major challenge is determining the optimal timing for transplant referral, as delayed referral may ultimately preclude transplantation because of the development of disease-related complications that compromise procedural success.

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Assessment and monitoring for markers of poor prognosis using the I NEED HELP mnemonic, as described previously, may facilitate timely referral and help avoid delayed transplantation.^{584,629-631} Clinical features such as persistent

NYHA class III or IV symptoms, inotrope dependence, and ventricular arrhythmias refractory to pharmacologic or invasive therapy are all associated with poor prognosis and should prompt strong consideration of heart transplant (Figure 8.3).⁶³⁰⁻⁶³²

Table 8.4 – Recommendations for the use of durable mechanical circulatory support

Recommendation	Strength of recommendation	Certainty of evidence
In patients with advanced HF who are not candidates for heart transplant, we recommend IN FAVOR OF durable mechanical circulatory support as destination therapy.	STRONG	MODERATE
In patients with advanced HF who are candidates for heart transplant but are expected to remain on the waiting list long enough to be at risk of clinical deterioration, we recommend IN FAVOR OF durable mechanical circulatory support as a bridge to transplant.	STRONG	LOW
In patients with advanced HF and refractory pulmonary hypertension, we recommend IN FAVOR OF durable mechanical circulatory support as a bridge to candidacy for transplant.	STRONG	LOW
In patients with advanced HF and a history of cancer in remission with curative potential, we recommend IN FAVOR OF durable mechanical circulatory support as a bridge to candidacy for transplant.	STRONG	LOW

HF: heart failure.

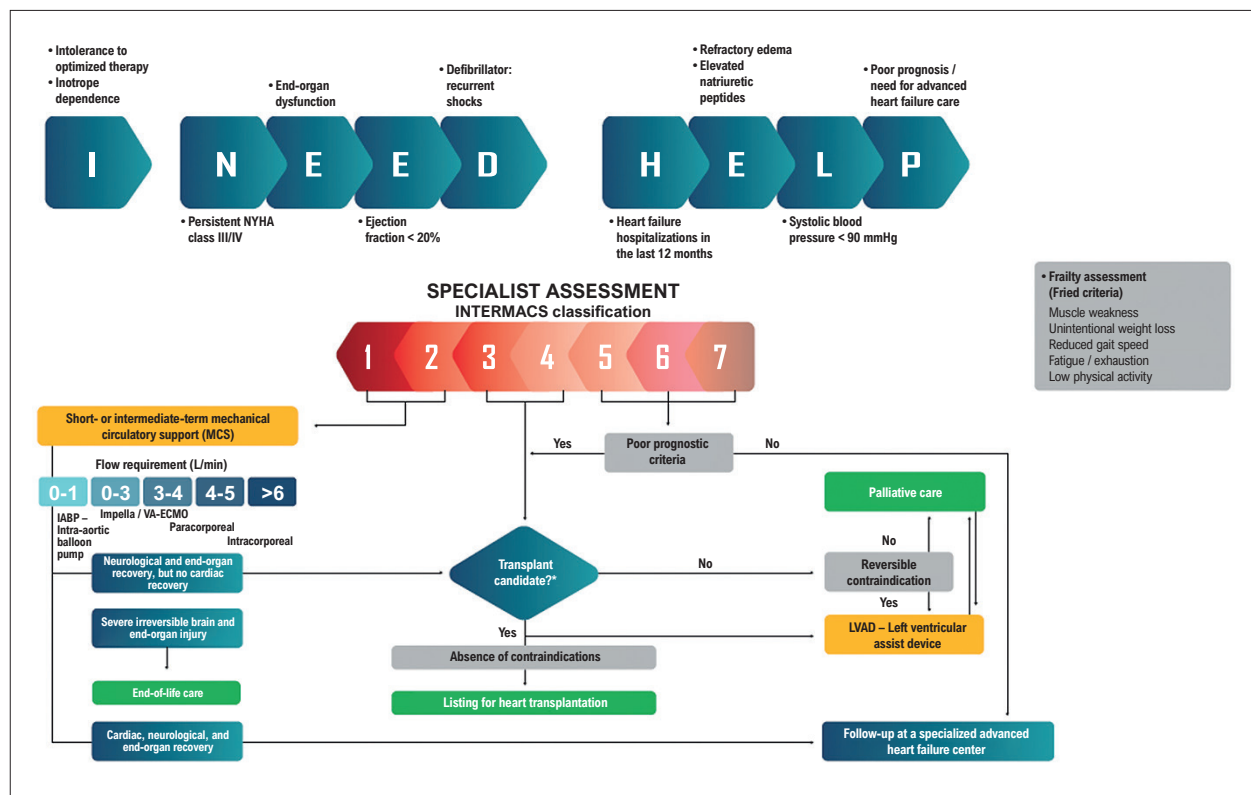


Figure 8.3 – Management algorithm for patients with advanced failure. * Frailty assessment using the modified Fried criteria (the presence of 3 of the following 5 criteria: unintentional weight loss of >4.5 kg during the previous year, loss of muscle mass and muscle weakness, fatigue/exhaustion, slow walking speed, and low physical activity) should be considered when evaluating candidacy for heart transplant. IABP: intra-aortic balloon pump; MCS: mechanical circulatory support; LVAD: left ventricular assist device; VA-ECMO: venoarterial extracorporeal membrane oxygenation; INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support; NYHA: New York Heart Association.

In outpatients with HF, peak VO_2 and V_E/VCO_2 slope have demonstrated prognostic value, predicting the risk of death, implantation of a durable MCS device, or the need for heart transplant.⁶³³ Chart 8.5 summarizes the clinical conditions in advanced HF that should prompt consideration of heart transplant.

In addition to these well-established indications for advanced HF therapies, some clinical scenarios warrant special consideration:

Patients with HCM and RCM have limited treatment options once they progress to advanced HF. Because these conditions are characterized by small ventricular cavities and restrictive physiology, they often respond poorly to inotropic therapy and/or durable mechanical circulatory support, making heart transplant an important therapeutic consideration.⁶³⁴⁻⁶³⁹

Patients with light-chain (AL) or transthyretin (ATTR) cardiac amyloidosis who develop advanced HF with severe symptoms may be candidates for heart transplant, depending on the extent of extracardiac organ involvement. In selected cases, heart transplant may be combined with liver transplant for ATTR amyloidosis or bone marrow transplant for AL amyloidosis. These strategies have been associated with improved quality of life and survival comparable to that observed in patients undergoing heart transplant for other causes of advanced HF.⁶⁴⁰⁻⁶⁴⁵

Infectious diseases: patients with HIV infection have post-transplant survival comparable to that of individuals without HIV, provided the infection is well controlled, with an undetectable viral load and a CD4 count > 200 cells. Likewise, patients with chronic hepatitis B or hepatitis C infection may be considered for heart transplant in the absence of cirrhosis and when the infection is adequately controlled; antiviral therapy should be continued.⁶⁴⁶

Once a patient has been identified as a candidate for heart transplant, a series of assessment steps is required to maximize the likelihood of a successful outcome. The first step includes clinical evaluation for markers of poor prognosis,^{581,583} objective functional assessment with CPET,^{98,647} invasive hemodynamic assessment,⁶⁴⁸ and the use of prognostic scores.⁶⁴⁹ The second step aims to identify conditions that may negatively impact post-transplant outcomes and, whenever possible, implement measures to mitigate their impact. Particular attention should be given to poorly controlled diabetes mellitus, irreversible pulmonary hypertension, severe cerebrovascular, renal, hepatic, or pulmonary disease, malignancy, and active smoking, all of which may compromise the success of heart transplant.

In summary, heart transplant remains the treatment of choice for patients who progress to advanced HF despite optimal GDMT and appropriate invasive therapy. However, achieving the full benefit of this therapy depends on the early recognition of high-risk features and timely referral to specialized centers.

8.5. End-of-Life Care (Palliative Care)

Given the poor prognosis associated with advanced HF, referral for palliative care should be considered early in the course of the disease, particularly after patients progress to stage D.⁶⁵⁰ In addition to managing physical and psychological symptoms, palliative care can facilitate shared decision-making regarding advanced therapies, such as heart transplant and durable LVADs, helping patients and caregivers understand the available treatment options, their risks and benefits, and the lifestyle adjustments required by these therapies.⁶⁵¹

Table 8.5 summarizes the recommendations for palliative care in patients with advanced HF.

Chart 8.5 – Clinical conditions in advanced heart failure that should prompt consideration of heart transplant

Clinical conditions
Dependence on inotropic therapy and/or mechanical circulatory support.
Persistent NYHA functional class III or class IV symptoms despite optimal medical therapy.
Symptomatic ventricular arrhythmias refractory to pharmacologic therapy, implantable cardiac devices, and/or catheter ablation.
Refractory angina with no option for revascularization.
CPET demonstrating peak $\text{VO}_2 \leq 12$ mL/kg/min in patients receiving beta-blockers; peak $\text{VO}_2 \leq 14$ mL/kg/min in patients intolerant to beta-blockers; or VE/VCO_2 slope > 35 mL (kg.min) during a submaximal CPET ($\text{RER} < 1.05$).
Special situations
Hypertrophic and/or restrictive cardiomyopathy refractory to medical therapy.
Transthyretin cardiac amyloidosis without a reasonable expectation of response to medical therapy.
Light-chain (AL) cardiac amyloidosis with controlled underlying hematologic disease.
Cardiac tumors with curative potential through cardiac explantation.
Controlled infectious diseases, including HIV infection (undetectable viral load and $\text{CD4} > 200$ cells/mm ³) and hepatitis B or C (without cirrhosis, portal hypertension, or hepatocellular carcinoma).

HF: heart failure; NYHA: New York Heart Association; VO_2 : oxygen consumption; VE/VCO_2 : minute ventilation/carbon dioxide production; CPET: cardiopulmonary exercise testing; RER: respiratory exchange ratio.

Table 8.5 – Recommendations for palliative care in patients with advanced heart failure

Recommendation	Strength of recommendation	Certainty of evidence
In patients with advanced heart failure who are being considered for advanced therapies, we recommend IN FAVOR OF evaluation by a palliative care team.	STRONG	LOW

9. Cardiovascular Comorbidities

9.1. Arrhythmias and Conduction Disturbances

9.1.1. Atrial Fibrillation

AF and HF are interrelated clinical conditions that are commonly regarded as having a “bidirectional relationship.” Each condition may cause or exacerbate the other through mechanisms such as structural cardiac remodeling, neurohormonal activation, and rate-related LV dysfunction.^{652,653}

The development of AF in patients with chronic HF is associated with a worse prognosis, including an increased risk of stroke and mortality.⁶⁵⁴ In patients with HF, the onset of AF is almost invariably associated with worsening quality of life and may serve as a marker of clinical progression.⁶⁵⁵

Approximately two-thirds of patients with HF are older than 65 years and are therefore more susceptible to AF and its associated complications. According to the Framingham Heart Study, HF increases the risk of AF by approximately 4.5-fold in men and 5.9-fold in women.⁶⁵⁶ In HFpEF, which is particularly common among older adults, the risk of developing AF may be up to 5.26-fold higher than in individuals without HFpEF.⁶⁵⁷ The EuroHeart Failure survey,⁶⁵⁸ conducted in 24 European countries, reported that up to 45% of patients with HF may have intermittent or established AF. The prevalence of AF also depends on the severity of the underlying heart disease, ranging from 10% to 20% in mild-to-moderate HF and reaching up to 50% in advanced HF.⁶⁵⁹⁻⁵⁶¹

Conversely, some patients initially develop AF and subsequently progress to HF (tachycardia-induced cardiomyopathy). These patients most often have persistent or permanent AF with poor ventricular rate control, either because of refractoriness to AV nodal blocking agents or because of frequent asymptomatic recurrences despite antiarrhythmic drug therapy or poor medication adherence. Improved control of ventricular response or cardiac rhythm, including invasive therapies such as catheter ablation and implantation of cardiac implantable electronic devices, may result in reverse cardiac remodeling. In this setting, the clinical course appears to be more favorable than that associated with other causes of HF.⁶⁶²

The treatment of patients with concomitant HF and AF includes the following steps: identification and treatment of potential causes or triggers of AF; treatment of HF; prevention of thromboembolic events; rate control; and rhythm control.

9.1.1.1. Identification of Triggers and Treatment of Heart Failure

Potential causes or precipitating factors, including hyperthyroidism, electrolyte disturbances, alcohol abuse, uncontrolled hypertension, mitral valve disease, myocardial ischemia, sleep apnea, and infection, should be identified and appropriately treated.

9.1.1.2. Prevention of Thromboembolic Events

Unless contraindicated, long-term oral anticoagulation is recommended for all patients with HF and AF, regardless of the AF pattern (paroxysmal, persistent, or permanent), taking into account the individual risk of stroke and systemic thromboembolism. For this purpose, we recommend using the updated CHA₂DS₂-VA score.⁶⁶³ Bleeding risk scores should be used only to guide the appropriate use of oral anticoagulants and should not be used to withhold anticoagulation therapy. By definition, all patients with HF and AF have a CHA₂DS₂-VA score of at least 1, and many have associated comorbidities that further increase thromboembolic risk. Therefore, most of these patients have an indication for long-term oral anticoagulation.

Direct oral anticoagulants (DOACs) are preferred over vitamin K antagonists (VKAs) for the prevention of thromboembolic events in patients with AF who do not have severe mitral stenosis or a mechanical prosthetic valve, as they provide similar efficacy with a lower risk of intracranial hemorrhage.^{487,664,665} LA appendage closure might be considered for patients with HF and AF who have contraindications to oral anticoagulation. However, RCTs evaluating this strategy did not include patients with clear contraindications to oral anticoagulants, and available evidence indicates outcomes comparable to those achieved with oral anticoagulation.⁶⁶⁶

9.1.1.3. Rate Control

Evidence regarding the optimal HR target in patients with AF and HF remains inconclusive. In patients with permanent AF in whom a rate-control strategy has already been adopted, maintaining a mean HR of approximately 80–85 bpm (as assessed by 24-hour Holter monitoring, for example) is required to reduce the risk of progression to tachycardia-induced cardiomyopathy. However, this level of rate control does not necessarily need to be strict.

The RACE II trial⁶⁶⁷ enrolled 614 patients with permanent AF who were randomly assigned to either a strict rate-control strategy (resting HR < 80 bpm) or a lenient rate-control strategy (resting HR < 110 bpm). After a maximum follow-

up of 3 years, no significant differences were observed between the groups in the primary composite outcome of cardiovascular mortality, HF hospitalization, stroke, systemic embolism, bleeding, or life-threatening arrhythmic events. Therefore, lenient rate control is an acceptable initial strategy; however, a stricter HR target should be pursued in patients with persistent symptoms or cardiac dysfunction likely attributable to tachycardia.

Beta-blockers may be used for rate control in patients with HFrEF or HFmrEF because of their well-established safety profile in these populations.⁶⁶⁸ Digoxin might be considered when HR remains elevated despite beta-blocker therapy or when beta-blockers are contraindicated or not tolerated.⁶⁶⁹ In patients with NYHA class IV HF and/or hemodynamic instability, intravenous amiodarone might be considered to AF with rapid ventricular response.⁶⁷⁰ In HFpEF, evidence supporting the efficacy of any specific rate-control agent is scarce.

The RATE-AF trial⁶⁷¹ compared digoxin with bisoprolol in patients with persistent AF and NYHA class II–IV HF symptoms. Compared with bisoprolol, digoxin produced similar improvements in quality of life at 6 months (primary outcome) and was associated with greater improvements in European Heart Rhythm Association (EHRA) symptom class and NYHA functional class. Only 19% of participants had an LVEF < 50%, indicating that most patients had HFmrEF or HFpEF. However, a subanalysis of a large RCT suggested that serum digoxin concentrations ≥ 1.2 ng/mL are associated with an increased risk of death in patients with HF and AF.⁶⁷²

AV node ablation followed by permanent pacemaker implantation might be considered in patients with AF and elevated ventricular rates, particularly in those who are not candidates for rhythm-control therapy with antiarrhythmic drugs and/or catheter ablation or in patients receiving biventricular CRT.^{673,674} Conventional RV pacing may increase the risk of AF and HF in patients with permanent pacemakers. Left bundle branch pacing of the His–Purkinje conduction system may reduce the adverse effects associated with conventional RV pacing.^{221,675} Additional information on cardiac pacing and AF is available in the 2023 Brazilian Guidelines for Cardiac Implantable Electronic Devices.⁶⁷⁶

9.1.1.4. Rhythm Control

In patients with DHF who have AF with rapid ventricular response and hemodynamic instability, urgent electrical cardioversion is indicated after consideration of the patient's thromboembolic risk. Cardioversion should also be considered to improve symptoms in patients with persistent symptomatic AF despite optimal medical therapy. In patients not receiving long-term oral anticoagulation with AF duration > 48 hours, at least 3–4 weeks of anticoagulation are required before cardioversion. If earlier cardioversion is planned or if there is uncertainty regarding adherence to DOAC therapy, TEE is recommended to exclude LA thrombus.⁶⁷⁷ When pharmacologic cardioversion is preferred, amiodarone

is the agent of choice. Other antiarrhythmic drugs have been associated with less favorable outcomes in patients with HFrEF.^{678,679} Amiodarone may also help maintain sinus rhythm after cardioversion in patients with HF.⁶⁸⁰ In addition, amiodarone is effective for pharmacologic conversion of AF to sinus rhythm, provided that patients are receiving optimal oral anticoagulant therapy.^{681,682}

Landmark RCTs comparing rate-control and rhythm-control strategies in patients with HF have not demonstrated the superiority of either approach.^{661,683,684} The AF-CHF trial⁶⁶¹ enrolled 1376 patients with HF and compared a rhythm-control strategy (682 patients) with a rate-control strategy (694 patients) over a mean follow-up of 37 months. At study completion, rhythm control did not reduce cardiovascular mortality compared with rate control (27% vs. 25%, respectively; $p = \text{NS}$). A major limitation of this trial was the limited use of interventional therapies, such as catheter ablation and cardiac implantable electronic devices, making it largely representative of pharmacologic management in routine clinical practice.

Catheter ablation has evolved substantially and has become an attractive treatment option for patients with AF and HF. The largest RCTs evaluating catheter ablation in this population have demonstrated reductions in both HF hospitalizations and mortality with an ablation-based strategy.^{685–688} The AATAC trial enrolled 203 patients with persistent AF, LVEF < 40%, and NYHA class II–III HF. Compared with amiodarone, catheter ablation significantly increased the likelihood of maintaining sinus rhythm at 24 months, reduced hospitalizations by 45%, and lowered mortality (8% vs. 18%).⁶⁸⁵

The CASTLE-AF trial randomly assigned 363 patients with paroxysmal or persistent AF, LVEF < 35%, NYHA class II–IV HF, and an ICD to either catheter ablation or standard medical therapy.⁶⁹⁵ The composite endpoint of death or HF hospitalization was lower in the ablation group (28.5%) than in the medical therapy group (44.6%). Mortality was also lower among patients in the ablation group.

A meta-analysis of 11 RCTs comparing rhythm-control and rate-control strategies found that patients treated with catheter ablation had improved survival (49% RRR) and fewer hospitalizations (56% RRR).⁶⁸⁷ These findings should be interpreted with caution, however, because the study populations were highly selected (363 of 3013 screened patients were enrolled in CASTLE-AF), the trials were open-label, crossover between treatment strategies was common, and the overall number of clinical events was relatively small. Moreover, these studies were conducted by highly experienced electrophysiology centers, and their results may not be fully reproducible in routine clinical practice.

Evidence has also emerged regarding catheter ablation in patients with advanced HF. The CASTLE-HTx trial⁶⁸⁸ was a prospective, single-center, open-label RCT that randomly assigned patients with HFrEF and AF to receive either catheter ablation plus GDMT ($n = 97$) or GDMT alone ($n = 97$). All participants were undergoing evaluation for either an LVAD or heart transplant. The trial was terminated early for the unexpected efficacy in the ablation group. The

primary composite endpoint of all-cause mortality, LVAD implantation, or urgent heart transplant was significantly less frequent in the ablation group. At 18 months, the primary endpoint occurred in 8% of patients in the ablation group compared with 30% of those in the medical therapy group ($p < 0.001$). Catheter ablation was also associated with significant improvements in secondary outcomes, including all-cause mortality (6% vs. 20%; HR, 0.29; 95% CI, 0.12–0.72; $p < 0.05$), LVAD implantation (1% vs. 10%; $p < 0.05$), urgent heart transplant (1% vs. 6%; $p > 0.05$), increase in LVEF at 12 months (+7.8% vs. +1.4%; $p < 0.05$), decrease in AF burden at 12 months (–31.4% vs. –8.6%; $p < 0.05$), and amiodarone use at 12 months (29% vs. 57%).

These findings reinforce the favorable results of the CASTLE-AF trial, which excluded patients listed for heart transplant. Although the single-center design and relatively small sample size of this study limit the generalizability of its findings, the results are nevertheless encouraging and support further investigation of catheter ablation for the management of AF in patients with advanced HF.

9.1.1.5. Treatment of Atrial Fibrillation Combined with Cardiac Pacing

When a rhythm-control strategy has failed or is not desired, and rapid ventricular rates persist despite optimal medical therapy after all other treatment options have been exhausted, AV node ablation followed by implantation of a CRT device might be considered as a treatment option. AV node ablation combined with pacing is a well-established strategy for patients with AF and difficult-to-control rates. Early studies using RV pacing demonstrated clinical benefit.⁶⁸⁹ However, when RV pacing was compared with CRT in more recent trials, particularly among patients with reduced LVEF, CRT consistently produced superior outcomes.⁶⁷³

The PAVE⁶⁹⁰ and BLOCK-HF²¹⁸ trials included patients with LVEF $> 35\%$, with mean LVEFs of 46% and 40%, respectively. In both trials, patients treated with CRT experienced better clinical outcomes than those receiving RV pacing. In the PAVE trial, patients with NYHA class II–III HF, a mean LVEF of 46%, and AF who underwent AV node ablation had greater improvement in the 6MWD and LVEF with CRT than with RV pacing.

Table 9.1 summarizes the recommendations for the treatment of AF in patients with HF.

9.1.2. Ventricular Arrhythmias

Ventricular arrhythmias are common in patients with HF and may cause symptoms such as palpitations, chest pain, dizziness, and syncope, lead to SCD through ventricular tachycardia or ventricular fibrillation, and contribute to the progression of ventricular dysfunction. An important and often controversial clinical issue is determining whether a high burden of premature ventricular complexes (PVCs) is the primary cause of HF. This concept applies only to selected patients with frequent monomorphic PVCs (typically with LBBB morphology) and should not be confused with

polymorphic PVCs secondary to underlying structural heart disease, for which there is no evidence that suppression results in reverse cardiac remodeling.

Several studies have demonstrated an association between a high burden of monomorphic PVCs and the development of LV dysfunction,⁶⁹¹ and reductions in PVC burden after catheter ablation have been associated with improvements in LVEF.⁶⁹² Although no precise threshold has been established to define therapeutic benefit, a PVC burden $> 24\%$ has been independently associated with an increased risk of tachycardia-induced cardiomyopathy.⁶⁹¹ A recent meta-analysis⁶⁹³ identified several predictors of PVC-induced cardiomyopathy, including age, a mean PVC burden of approximately 17%, the presence of nonsustained ventricular tachycardia, an epicardial or LV origin of the PVCs, and interpolated PVCs.

Approach to patients with HF and ventricular arrhythmias should begin with the identification and correction of electrolyte and metabolic abnormalities, as well as discontinuation of medications with proarrhythmic potential. It is important to recognize that the main therapeutic approach in these conditions is optimal GDMT for HF, using the recommended drug combinations and target doses in accordance with current guidelines, particularly beta-blockers, MRAs, sacubitril-valsartan, and SGLT2 inhibitors. The role of antiarrhythmic drugs is limited. Amiodarone is the only antiarrhythmic agent considered acceptable in patients with HF. Although it does not reduce the risk of SCD, it may alleviate symptoms and decrease the frequency of ICD shocks.⁶⁹⁴

Catheter ablation may be beneficial in patients with persistent, limiting symptoms despite optimal medical therapy, in those requiring reduction of recurrent ICD shocks, or in patients with frequent or incessant sustained ventricular arrhythmias.⁶⁹⁵

9.1.3. Symptomatic Bradycardia, Pauses, and Atrioventricular Block

The indications for permanent pacemaker therapy in patients with HF are the same as those for patients with other cardiovascular diseases. However, substantial evidence indicates that RV pacing may adversely affect LV systolic function, potentially leading to HF in the long term.⁶⁹⁶ Patients with HFrEF who require a high burden of ventricular pacing (eg, AV block or AF with slow ventricular response) should receive CRT rather than a conventional pacemaker to reduce the risk of adverse clinical outcomes.⁶⁹⁷

As a more physiological alternative to conventional RV pacing, CSP has been increasingly adopted. In a nonrandomized study comparing 304 consecutive patients who underwent His bundle pacing with 433 consecutive patients treated with conventional RV pacing, those receiving His bundle pacing experienced fewer HF hospitalizations and showed a trend toward lower mortality.⁶⁹⁸ Although this approach is promising, additional evidence is needed to establish its long-term effectiveness, define the risk of procedural complications, and determine the expertise required for its routine implementation.

Table 9.1 – Recommendations for the treatment of atrial fibrillation in patients with heart failure

Recommendation	Strength of recommendation	Certainty of evidence
In all patients with AF and concomitant HF, we recommend IN FAVOR OF the use of oral anticoagulants, with DOACs preferred (except in patients with moderate-to-severe mitral stenosis or mechanical prosthetic valves) to prevent ischemic stroke.	STRONG	HIGH
In patients with HF and AF, we recommend IN FAVOR OF the use of beta-blockers for short-term and long-term rate control.	STRONG	MODERATE
We recommend IN FAVOR OF the use of digoxin for rate control when HR remains elevated despite beta-blocker therapy or when beta-blockers are contraindicated or not tolerated.	STRONG	MODERATE
In patients with AF receiving beta-blockers and/or digoxin, we recommend IN FAVOR OF the use of oral amiodarone when HR cannot be adequately controlled.	WEAK	LOW
In patients with AF requiring rapid ventricular rate control, we recommend IN FAVOR OF intravenous administration of digoxin or amiodarone for rate control in the absence of pre-excitation.	STRONG	MODERATE
In patients with DHF who present with AF, rapid ventricular rates, and hemodynamic instability, we recommend IN FAVOR OF urgent electrical cardioversion.	STRONG	LOW
In patients with AF, we recommend IN FAVOR OF the use of amiodarone to restore and maintain sinus rhythm.	STRONG	MODERATE
In patients with HF and AF, we recommend IN FAVOR OF restoration and maintenance of sinus rhythm, individualized according to patient needs, clinical characteristics, and symptoms.	STRONG	HIGH
In patients with AF and advanced HF, we recommend IN FAVOR OF catheter ablation to reduce hospitalizations for DHF and mortality.	STRONG	MODERATE
We recommend IN FAVOR OF rate control through atrioventricular node ablation combined with permanent pacemaker implantation when pharmacologic therapy is ineffective or associated with adverse effects.	WEAK	LOW
In patients with a clear association between paroxysmal or persistent AF and worsening HF symptoms despite GDMT, we recommend IN FAVOR OF catheter ablation for the prevention or treatment of AF.	STRONG	MODERATE
In patients with AF and HF, we recommend AGAINST the use of digitalis glycosides as monotherapy for ventricular rate control.	STRONG	MODERATE
In patients with HFrEF and AF, we recommend AGAINST the use of nondihydropyridine calcium channel blockers for rate control.	STRONG	LOW

AF: atrial fibrillation; HF: heart failure; DOACs: direct oral anticoagulants; HR: heart rate; GDMT: guideline-directed medical therapy; HFrEF: heart failure with reduced ejection fraction.

9.2. Chronic Coronary Syndromes

9.2.1. Medical Therapy

CAD is the leading cause of HF in Brazil, as in many other countries.⁴³³ Optimal management of HF, particularly HFrEF, includes several classes of medications that also positively impact the natural history of CAD, including beta-blockers, RAAS inhibitors, and SGLT2 inhibitors, such as empagliflozin and dapagliflozin. However, not all drugs used to treat anginal symptoms are appropriate or safe for patients with HFrEF.^{125,127,699-704}

Beta-blockers are recommended for the treatment of anginal symptoms in patients with HFrEF. In patients with a resting HR ≥ 70 bpm despite optimal beta-blocker therapy

in HFrEF, or in those who are intolerant to beta-blockers, ivabradine may be used to reduce hospitalizations and relieve symptoms.^{163,705} In patients who remain symptomatic despite treatment with beta-blockers and/or ivabradine, other antianginal agents might be considered, including nitrates, dihydropyridine CCBs, such as amlodipine, and ranolazine. These agents are used to relieve anginal symptoms, although their effects on clinical outcomes are either neutral or unproven, and they should be prescribed cautiously in patients at risk of symptomatic hypotension.⁷⁰⁶⁻⁷⁰⁸ Trimetazidine, when added to beta-blocker therapy in patients with angina, appears to provide additional improvements in LV systolic function and exercise capacity.⁷⁰⁹⁻⁷¹¹ In contrast, nondihydropyridine CCBs, such as diltiazem and verapamil, are contraindicated in HFrEF

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because of their negative inotropic effects and substantial potential to increase the risk of cardiovascular death.⁷¹²

Pharmacologic secondary prevention with aspirin and high-intensity statins, with or without ezetimibe, reduces major cardiovascular events, including myocardial infarction, cardiovascular death, and hospitalizations, and should be prescribed for patients with HF and CAD, regardless of LV systolic function.⁷¹³⁻⁷¹⁵ In patients without an indication for long-term oral anticoagulation, vascular-dose rivaroxaban (2.5 mg twice daily) combined with aspirin did not reduce the composite outcome of death, myocardial infarction, or stroke in patients with HFrEF.⁷¹⁶ However, it was associated with a reduction in ischemic events in patients with HFpEF.⁷¹⁷

In patients with HFpEF, beta-blockers, long-acting nitrates, CCBs, ivabradine, ranolazine, trimetazidine, and combinations of these agents might be considered for the relief of angina. However, there is no evidence that these therapies improve HF-related or coronary outcomes.

Table 9.2 summarizes the recommendations for the pharmacologic treatment of anginal symptoms in patients with HF.

9.2.2. Myocardial Revascularization

Coronary revascularization, whether performed by coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI), is frequently indicated for patients with HF who have angina, reflecting the high prevalence of CAD in this population. Revascularization

should be considered in selected patients with HF and anginal symptoms.

The STICH trial, which compared CABG with optimal medical therapy, demonstrated that, after 10 years of follow-up, CABG was associated with significant reductions in all-cause mortality, cardiovascular mortality, and hospitalizations in patients with LVEF $\leq 35\%$.⁷¹⁸ In contrast, the REVIVED-BCIS2 trial, which compared PCI with medical therapy in patients with HFrEF, showed no benefit with PCI in terms of mortality, hospitalizations, myocardial infarction, LVEF at 12 months, or SCD.⁷¹⁹

A propensity score analysis demonstrated that CABG provides clinical benefit in patients with diabetes mellitus and LV dysfunction, with lower rates of mortality and major adverse cardiovascular events.⁷²⁰ Surgical revascularization is associated with better outcomes in patients with moderate-to-severe LV dysfunction who have left main coronary artery disease or complex CAD.^{4,721,722} Surgical ventricular reconstruction, when performed in conjunction with CABG, may be beneficial in patients with refractory HF, a large LV intracavitary thrombus, or persistent arrhythmias resulting from a ventricular aneurysm.^{494,723,724}

Table 9.3 summarizes the recommendations for myocardial revascularization in patients with HFrEF.

9.3. Valvular Heart Disease

GDMT should be provided to all patients with HF and valvular heart disease as part of a multidisciplinary approach that includes specialists in valvular heart disease.

Table 9.2 – Recommendations for the pharmacologic treatment of anginal symptoms in patients with heart failure

Recommendation	Strength of recommendation	Certainty of evidence
In patients with HFrEF, we recommend IN FAVOR OF the use of beta-blockers (carvedilol, metoprolol succinate, or bisoprolol) for the control of anginal symptoms.	STRONG	HIGH
In patients with HFrEF in sinus rhythm and HR > 70 bpm despite optimal beta-blocker therapy, we recommend IN FAVOR OF the use of ivabradine for the control of anginal symptoms.	WEAK	LOW
In patients with HFrEF who remain symptomatic despite treatment with beta-blockers and/or ivabradine, we recommend IN FAVOR OF the use of other antianginal agents, such as dihydropyridine CCBs (amlodipine), nitrates, or ranolazine.	WEAK	LOW
In patients who remain symptomatic despite treatment with beta-blockers and/or ivabradine, we recommend IN FAVOR OF the use of trimetazidine to improve symptoms, functional capacity, and left ventricular systolic function.	WEAK	LOW
In patients with HFpEF in sinus rhythm and concomitant atherosclerotic coronary artery disease or peripheral artery disease who are at high risk of stroke and low risk of bleeding, we recommend IN FAVOR OF the use of vascular-dose rivaroxaban (2.5 mg twice daily) to reduce ischemic events.	WEAK	LOW
We recommend AGAINST the use of nondihydropyridine CCBs (diltiazem or verapamil).	STRONG	MODERATE

HFrEF: heart failure with reduced ejection fraction; HR: heart rate; CCB: calcium channel blocker; HFpEF: heart failure with preserved ejection fraction.

Table 9.3 – Recommendations for myocardial revascularization in patients with heart failure with reduced ejection fraction

Recommendation	Strength of Recommendation	Certainty of evidence
In patients with HF and LVEF $\leq 35\%$, we recommend IN FAVOR OF CABG to improve anginal symptoms and reduce subsequent revascularization procedures and mortality.	STRONG	MODERATE
In patients with HFrEF, persistent anginal symptoms despite optimal medical therapy, and severe proximal coronary lesions amenable to revascularization, we recommend IN FAVOR OF CABG.	STRONG	MODERATE
We recommend IN FAVOR OF PCI as an alternative to CABG following Heart Team discussion, taking into account coronary anatomy, comorbidities, and surgical risk.*	WEAK	LOW
In patients with HFrEF without angina, we recommend AGAINST the use of myocardial viability as the sole criterion for the indication of myocardial revascularization.	WEAK	MODERATE

*Note: *Criteria associated with increased surgical risk are listed in Chart 9.1. HF: heart failure; LVEF: left ventricular ejection fraction; CABG: coronary artery bypass grafting; HFrEF: heart failure with reduced ejection fraction; PCI: percutaneous coronary intervention.*

9.3.1. Aortic Stenosis

AS may cause or worsen HF symptoms by increasing LV afterload, while medical therapy alone has little impact on mortality. Approximately 30% of patients with severe AS have LV systolic dysfunction (LVEF $< 50\%$).^{725,726}

In patients with symptomatic severe AS (aortic valve area $\leq 1.0 \text{ cm}^2$ and mean transvalvular gradient $\geq 40 \text{ mmHg}$), aortic valve intervention is recommended regardless of LVEF.

Patients with symptomatic HF and suspected low-flow, low-gradient severe AS (mean gradient $< 40 \text{ mmHg}$ and peak aortic jet velocity $< 4.0 \text{ m/s}$) with LVEF $> 50\%$ and a high aortic valve calcium score might be considered for surgical aortic valve replacement (SAVR) or TAVI following Heart Team discussion.

The following aortic valve calcium score thresholds support the diagnosis of severe AS:

- Highly likely severe AS:
 - ≥ 3000 in men
 - ≥ 1600 in women
- Likely severe AS:
 - ≥ 2000 in men
 - ≥ 1200 in women
- Unlikely severe AS
 - ≤ 1600 in men
 - ≤ 800 in women

In patients with symptomatic HF, suspected low-flow, low-gradient AS (mean gradient $< 40 \text{ mmHg}$ and peak aortic jet velocity $< 4.0 \text{ m/s}$), and LVEF $< 50\%$, assessment of contractile reserve with dobutamine stress echocardiography is recommended to guide clinical decision-making. Cardiac computed tomography for quantification of the aortic valve calcium score is also recommended to confirm the severity of AS.⁷²⁵⁻⁷²⁷

Among patients with contractile reserve in whom severe AS is confirmed, SAVR or TAVI is recommended following Heart Team discussion. In patients with contractile reserve but without confirmation of severe AS, optimal GDMT is recommended.

Patients without contractile reserve but with high aortic valve calcium scores might be considered for SAVR or TAVI. Patients without contractile reserve and without elevated aortic valve calcium scores should be treated with medical therapy.

Chart 9.1 – Criteria indicative of high surgical risk in patients with heart failure

High-risk patient – Criteria
Advanced heart failure with end-organ damage
Dependence on intravenous inotropic therapy
Use of temporary mechanical circulatory support
Poor coronary bed
Marked left ventricular dilation
Left ventricular aneurysm
Left ventricular ejection fraction $< 25\%$
Significant mitral regurgitation
Significant tricuspid regurgitation
Right ventricular dysfunction
Significant comorbidities
Radiation-induced heart disease
Frailty
Unavailability of mechanical circulatory support resources

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Reduced LVEF is associated with increased mortality in patients with moderate and severe AS, irrespective of symptoms, even after valve intervention.⁷²⁸⁻⁷³¹ In the PARTNER trial,⁷³² which enrolled patients at high surgical risk, 31.9% had LVEF < 50%. These patients had similar 30-day and 1-year all-cause mortality compared with those with preserved LVEF. However, among patients with LV dysfunction, approximately 30% failed to demonstrate improvement in LVEF after intervention and had a 3-fold higher 1-year mortality. Furthermore, LVEF was an independent predictor of cardiovascular mortality at 2 years after TAVI.

Prospective observational studies using CMR in patients with severe AS have shown that increasing myocardial fibrosis is a strong predictor of adverse prognosis.

There is broad consensus regarding the indications for intervention in patients with AS. These include the presence of symptoms identified from the clinical history or abnormal findings on exercise testing or stress echocardiography, anatomically severe AS, reduced LVEF, or elevated NP levels.⁷³² Decisions regarding the timing and type of intervention should be made through shared decision-making within a Heart Team. The Heart Team should carefully weigh the benefits and risks of each approach, taking into account the patient's age, life expectancy, clinical characteristics, and anatomical factors.

However, recommendations for asymptomatic patients with severe AS and reduced LVEF are based primarily on clinical experience and expert opinion.^{733,734} Likewise, evidence remains limited for patients with low-flow, low-gradient AS and LVEF < 35%. A recent meta-analysis found only a weak association between LVEF and mortality but demonstrated a robust benefit of early valve intervention in patients with reduced LVEF.⁷³⁵

Table 9.4 summarizes the recommendations for the treatment of AS in patients with HF.

9.3.2. Aortic Regurgitation

Severe aortic regurgitation (AR) results in progressive LV dilation, eventually leading to LV dysfunction and HF

symptoms. The natural history of patients with severe AR and low LVEF managed conservatively is poor.⁷³⁶ Although LVEF is an important prognostic determinant after surgery, the long-term outcomes of patients with severely reduced LVEF remain incompletely understood.^{737,738} However, surgical intervention should be encouraged in these patients.⁷³⁸ Quantification of myocardial fibrosis by CMR has emerged as a promising tool for determining the optimal timing of intervention.⁷³⁹

In symptomatic patients with severe AR who do not have prohibitive surgical risk, aortic valve intervention is recommended regardless of LVEF.^{738,740}

In asymptomatic or minimally symptomatic patients with severe AR, an LV end-systolic diameter > 50 mm, or > 25 mm/m² when indexed to body surface area, is associated with worse clinical outcomes and should prompt referral for surgery. The same recommendation applies to patients with LVEF ≤ 50%.^{738,741,742}

Table 9.5 summarizes the recommendations for intervention in patients with HF and AR.

9.3.3. Secondary Mitral Regurgitation

MR is common in patients with HF and contributes to worsening dyspnea and exercise intolerance. Secondary MR is an independent predictor of poor prognosis in HF because it promotes adverse cardiac remodeling and is associated with its complicating factors, such as AF, pulmonary hypertension, and ventricular dysfunction.⁷⁴³ The management of secondary MR is discussed in a separate section of this guideline.

9.3.4. Secondary Tricuspid Regurgitation

The severity of secondary TR is dynamic and depends on RV function and the presence of pulmonary hypertension. Management should focus on treating the underlying cause, including pulmonary hypertension, RV failure, and HFrEF. Patients with refractory TR should be referred to a Heart Team for consideration of valve intervention. This topic is discussed in detail in the appropriate chapter of this guideline addressing interventions for HFrEF.

Table 9.4 – Recommendations for the treatment of aortic stenosis in patients with heart failure

Recommendation	Strength of recommendation	Certainty of evidence
In symptomatic patients with severe AS (aortic valve area ≤ 1.0 cm ² and mean transvalvular gradient ≥ 40 mm Hg), we recommend IN FAVOR OF SAVR or TAVI, regardless of LVEF.	STRONG	HIGH
In symptomatic patients with HF, severe low-flow, low-gradient AS, LVEF < 50%, and preserved left ventricular contractile reserve, we recommend IN FAVOR OF SAVR or TAVI to improve symptoms and reduce mortality.	STRONG	HIGH
In patients with symptomatic HF, suspected severe low-flow, low-gradient AS (mean gradient < 40 mm Hg and peak aortic jet velocity < 4.0 m/s), LVEF > 50%, and a high aortic valve calcium score, SAVR or TAVI might be considered following Heart Team discussion.	STRONG	MODERATE

AS: aortic stenosis; SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve implantation; LVEF: left ventricular ejection fraction; HF: heart failure.

Table 9.5 – Recommendations for intervention in patients with heart failure and aortic regurgitation

Recommendation	Strength of recommendation	Certainty of evidence
In patients with symptomatic HF and severe AR who do not have prohibitive surgical risk, we recommend IN FAVOR OF SAVR or TAVI following Heart Team discussion.	STRONG	HIGH
In asymptomatic or minimally symptomatic patients with severe AR, a left ventricular end-systolic diameter >50 mm or >25 mm/m ² when indexed to body surface area, or LVEF ≤50%, we recommend IN FAVOR OF SAVR or TAVI following Heart Team discussion.	STRONG	HIGH

HF: heart failure; AR: aortic regurgitation; SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve implantation; LVEF: left ventricular ejection fraction.

9.4. Systemic Arterial Hypertension

Hypertension is widely recognized as one of the most important modifiable risk factors for the development of HF across the entire spectrum of LVEF. Its impact is particularly pronounced in HFpEF, in which the prevalence of hypertension ranges from 60% to 89% across different populations.^{474,744} Data from the Framingham Heart Study showed that 91% of patients with HF had a history of hypertension during the 20 years preceding diagnosis.^{745,746} Other epidemiological studies have demonstrated that hypertension doubles the risk of HF in men and triples the risk in women, accounting for 39% of HF cases in men and 59% in women.⁷⁴⁷

Despite this well-established association, RCTs specifically evaluating antihypertensive treatment strategies or BP targets in patients with HF and hypertension have not been conducted.⁴ Available evidence suggests that lowering BP, particularly targeting an SBP < 120 mm Hg, is associated with a lower incidence of HF in the general population.³¹¹ Conversely, in patients with HFREF, hypotension, even when unrelated to antihypertensive therapy, is associated with worse clinical outcomes, likely reflecting the consequences of low cardiac output rather than adverse effects of treatment.³⁰⁹ Therefore, the management of HFREF is generally similar in patients with and without hypertension. BP thresholds and treatment targets should follow current cardiovascular prevention guidelines, provided they are well tolerated.¹¹

Recent European guidelines emphasize the use of pharmacologic therapies with proven outcome benefits in HFREF, including ACEIs, ARBs, ARNIs, beta-blockers, MRAs, and SGLT2 inhibitors.³⁰⁹ In contrast, among patients with HFpEF, elevated BP remains an important marker of cardiovascular risk, whereas low BP, particularly during sleep, has been associated with increased mortality in patients with HFREF or HFmrEF.⁷⁴⁸

10. Noncardiovascular Comorbidities

10.1. Diabetes

Diabetes mellitus is a well-established risk factor for HF independent of CAD. Moreover, HF is one of the most common initial manifestations of cardiovascular disease in patients with diabetes and may present as HFREF, HFmrEF, or HFpEF.^{744,749-757} Therefore, routine screening for HF should

be performed in patients with diabetes, including assessment for signs and symptoms of HF at every clinical visit, periodic measurement of biomarkers (BNP or NT-proBNP), and ECG and echocardiography when clinically indicated.

The SGLT2 inhibitors empagliflozin, dapagliflozin, canagliflozin, and sotagliflozin have demonstrated benefits in preventing HF hospitalizations, major adverse cardiovascular events, renal dysfunction, and cardiovascular death in patients with diabetes and cardiovascular risk factors or established cardiovascular disease, based on the EMPA-REG OUTCOME, DECLARE-TIMI 58, CANVAS, and SCORED trials.^{155,703,704,758} A meta-analysis including 90,409 participants (82.7% with diabetes) from 13 RCTs evaluating SGLT2 inhibitors in 3 high-risk populations (patients with type 2 diabetes and high cardiovascular risk, HF, or CKD) demonstrated additional benefits in reducing CKD progression and acute kidney injury, not only among patients with diabetes and high cardiovascular risk but also in those with CKD or HF.⁷⁵⁹ Therefore, SGLT2 inhibitors should be considered the preferred first-line glucose-lowering therapy, either alone or in combination with metformin, in patients with HFREF.

The selective MRA finerenone has been evaluated in 2 RCTs involving patients with diabetic nephropathy. The FIDELIO-DKD trial enrolled 5734 patients with CKD (urinary albumin-to-creatinine ratio [UACR] of 30–300 mg/g and eGFR of 25–60 mL/min/1.73 m² with diabetic retinopathy, or UACR of 300–5000 mg/g and eGFR 25–75 mL/min/1.73 m²) and type 2 diabetes, who were randomly assigned to receive finerenone (10–20 mg once daily) or placebo for a median follow-up of 2.6 years. All patients were treated with RAAS blockade at the maximum tolerated doses. The primary composite outcome was kidney failure, a sustained decrease of ≥ 40% in the eGFR from baseline, or death from renal causes. The key secondary composite outcome included cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or HF hospitalization. The primary outcome occurred in 17.8% of the finerenone group and in 21.1% of the placebo group (HR, 0.82; 95% CI, 0.73–0.93; p = 0.001). The secondary outcome occurred in 13.0% and 14.8%, respectively (HR, 0.86; 95% CI, 0.75–0.99; p = 0.03), although no significant reduction in HF hospitalization was observed.⁷⁶⁰

The FIGARO-DKD trial randomly assigned 7437 patients with type 2 diabetes and stage I–IV CKD to receive finerenone (10–20 mg once daily) or placebo for a median follow-up

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of 3.4 years. All patients were treated with RAAS blockade at the maximum tolerated doses. The primary composite outcome was cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and HF hospitalization. The secondary composite outcome included kidney failure, a sustained decrease of $\geq 40\%$ in the eGFR from baseline, or death from renal causes. The primary outcome occurred in 12.4% of the finerenone group and in 14.2% of the placebo group (HR, 0.87; 95% CI, 0.76–0.98; $p = 0.03$), primarily driven by a reduction in HF hospitalizations (HR, 0.71; 95% CI, 0.56–0.90).⁷⁶¹

A prespecified pooled analysis of these 2 RCTs, the FIDELITY analysis, included 13,026 patients with diabetic nephropathy followed for a mean of 3.0 years. The time-to-event efficacy outcome was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or HF hospitalization, and a composite of kidney failure, a sustained decrease of $\geq 57\%$ in the eGFR from baseline after 4 weeks, or death from renal causes. The composite cardiovascular outcome occurred in 12% of patients receiving finerenone and 14.4% of those receiving placebo (HR, 0.86; 95% CI, 0.78–0.95; $p = 0.0018$). HF hospitalization alone was significantly reduced with finerenone (HR, 0.86; 95% CI, 0.66–0.92; $p = 0.0030$).⁷⁶²

Based on these findings, finerenone is recommended for patients with type 2 diabetes and different stages of nephropathy to prevent HF hospitalizations (Table 10.1).

In the STEP-HFpEF DM trial, patients with obesity, type 2 diabetes, and HFpEF treated with semaglutide experienced a 7.3-point greater improvement in the KCCQ-CSS compared with placebo after 52 weeks (95% CI, 4.1–10.4; $p < 0.001$). Semaglutide also improved the 6MWD by 14.3 m relative to

placebo (95% CI, 3.7–24.9; $p = 0.008$). In addition, serious adverse events were less frequent in the semaglutide group (17.7% vs. 28.8%).

10.1.1. Glucose-Lowering Medications

Observational and case-control studies have shown that metformin is effective and safe in patients with diabetes and HF and is associated with a lower risk of death and HF hospitalization than sulfonylureas or insulin, provided that eGFR is ≥ 30 mL/min/1.73 m².^{763–765} Evidence regarding the effects of sulfonylureas in HF is inconsistent, with some studies suggesting harm,^{766,767} whereas the UK Prospective Diabetes Study (UKPDS) found no increased risk.⁷⁶⁸

Among dipeptidyl peptidase-4 (DPP-4) inhibitors, alogliptin, sitagliptin, and linagliptin were not associated with an increased risk of HF events.^{769–771} Vildagliptin was associated with increased ventricular volumes in a small study. Therefore, DPP-4 inhibitors should be used with caution in patients with HF.⁷⁷² Saxagliptin increased the risk of HF hospitalization by 27%,⁷⁷³ whereas thiazolidinediones increased the risk of developing HF, death from HF, and HF hospitalization.^{774–776} Insulin may promote fluid retention and has been associated with worse outcomes in patients with HF.⁷⁷⁷

10.2. Thyroid Disorders

Thyroid dysfunction, both hypothyroidism and hyperthyroidism may cause or precipitate HF.⁷⁷⁹ In a prospective cohort of 5599 patients with HF followed for a median of 434 days, higher TSH levels were associated with an increased incidence of HF events, including mortality (HR, 1.36; 95% CI, 1.08–1.71; $p = 0.002$).⁷⁸⁰

Table 10.1 – Recommendations for the treatment of diabetes in heart failure

Recommendation	Strength of recommendation	Certainty of evidence
In patients with type 2 diabetes and cardiovascular risk factors for atherosclerosis or established atherosclerotic cardiovascular disease, we recommend IN FAVOR OF the use of SGLT2 inhibitors (canagliflozin, dapagliflozin, or empagliflozin) to prevent HF hospitalization, major adverse cardiovascular events, renal dysfunction, and cardiovascular death.	STRONG	HIGH
In patients with HF, we recommend IN FAVOR OF the use of SGLT2 inhibitors (dapagliflozin or empagliflozin), with or without metformin, as initial glucose-lowering therapy to reduce HF hospitalizations and cardiovascular death.	STRONG	HIGH
In patients with type 2 diabetes and CKD, we recommend IN FAVOR OF the use of SGLT2 inhibitors to reduce the risk of HF hospitalization or cardiovascular death.	STRONG	HIGH
In patients with type 2 diabetes and different stages of nephropathy, we recommend IN FAVOR OF the use of finerenone to prevent HF hospitalizations.	STRONG	MODERATE
In patients with HFpEF, obesity, and diabetes, we recommend IN FAVOR OF the use of semaglutide to improve HF symptoms and functional capacity.	STRONG	MODERATE
In patients with HF and diabetes, we recommend AGAINST the use of saxagliptin and thiazolidinediones.	STRONG	MODERATE

HF: heart failure; SGLT2: sodium–glucose cotransporter 2; CKD: chronic kidney disease; HFpEF: heart failure with preserved ejection fraction.

Another observational study evaluated the effects of thyroid function in 1365 patients with HF (mean age, 57 years; 35% women; 45% in NYHA class II and 32% in NYHA class III). The primary composite outcome was LVAD implantation, heart transplant, and death. TSH levels ≥ 7 mIU/L were associated with a higher incidence of the composite outcome (HR, 3.25; 95% CI, 1.96–5.39; $p < 0.001$). Management should follow disease-specific thyroid guidelines. In general, thyroid hormone replacement therapy is recommended when TSH levels are ≥ 7 mIU/L.⁷⁸¹

10.3. Obesity

Obesity is associated with a worse prognosis in patients with HF, including both HFrEF and HFpEF. Recent studies have demonstrated clinical benefits of obesity treatment in patients with HFpEF, and the corresponding recommendations are discussed in the section on HFpEF management in this guideline. However, there are currently no adequately designed studies evaluating the impact of obesity treatment in patients with HFrEF, precluding a specific recommendation for this population.

10.4. Cachexia, Sarcopenia, and Frailty in Heart Failure

Cachexia is defined as involuntary weight loss occurring in several chronic diseases, including HF. According to the Evans criteria, cachexia is objectively defined as $\geq 5\%$ unintentional weight loss during the previous 12 months or BMI < 20 kg/m², in the presence of a chronic disease, including HF, and 3 or more of the following criteria: decreased muscle strength, fatigue, anorexia, low fat-free mass index, and laboratory abnormalities (anemia, low serum albumin, or increased inflammatory markers).⁷⁸²

Sarcopenia is defined as a primarily age-dependent decline in skeletal muscle mass, muscle strength, and physical performance.⁷⁸³ Frailty, in turn, is defined as a decline in an individual's physical and cognitive reserve that prohibits regulatory bodily mechanisms to counter or recover from acute stress.⁷⁸⁴ Frailty encompasses physical, cognitive, social, and psychological domains and affects 40% to 80% of patients with HF, occurring in up to 90% of those with HFpEF⁷⁸⁵ and 30% to 60% of those with HFrEF.⁷⁸⁶

To date, no RCTs have successfully demonstrated the benefit of specific interventions for patients with HF and cachexia, sarcopenia, or frailty. However, some studies have established the prognostic impact of these conditions. A meta-analysis of 9 studies found that cachexia increased the risk of all-cause mortality by 59% and more than doubled the risk of major adverse cardiovascular events (HR, 2.41; 95% CI, 1.50–3.85).⁷⁸⁷ Another systematic review and meta-analysis

including 21 studies and 68,556 patients with HF showed that sarcopenia was associated with a nearly 3-fold increase in the risk of adverse outcomes, particularly among patients with HFrEF (HR, 2.77; 95% CI, 1.29–5.95).⁷⁸⁸

Regarding frailty, a systematic review and meta-analysis of 32 studies involving 406,269 patients with HF demonstrated a 73% increase in mortality and a 96% increase in the risk of unplanned hospitalizations among patients with frailty.⁷⁸⁹

The prospective FRAGILE-HF study evaluated the influence of frailty and its individual domains in hospitalized patients with HF and demonstrated that outcomes progressively worsened as the number of frailty domains increased.⁷⁹⁰

A subanalysis of the FRAGILE-HF study showed that patients with both sarcopenia and cachexia had a markedly worse prognosis, with a nearly 3-fold higher mortality than patients with either condition alone or neither condition.⁷⁹¹

Table 10.2 summarizes the recommendations for the assessment of frailty in patients with HF.

10.5. Anemia and Iron Deficiency in Heart Failure

According to the World Health Organization (WHO) criteria, anemia is defined as a hemoglobin concentration < 12 g/dL in women and < 13 g/dL in men.

In HF, the prevalence of anemia is estimated at 30% in outpatients and up to 50% in patients with DHF.⁷⁹² Anemia in HF has a multifactorial etiology, including reduced erythropoietin production, iron deficiency, and chronic inflammation.⁷⁹³

A recent systematic review and meta-analysis showed that patients with DHF and anemia have a higher risk of both short-term mortality (odds ratio [OR], 1.91 at 30 days) and long-term mortality (OR, 1.72 at 1 year).⁷⁹⁴ A subanalysis of the TOPCAT trial demonstrated increased morbidity and mortality in patients with HFpEF and anemia.⁷⁹⁵ To date, no RCTs have established the optimal treatment strategy for anemia in patients with HF. Blood transfusion should generally be reserved for patients with hemodynamic instability or hemoglobin levels < 7.0 g/dL, when clinically indicated.⁷⁹²

Iron deficiency is present in approximately 50% of patients with chronic HF and is associated with poorer quality of life and functional capacity.^{793,796} It is defined as serum ferritin < 100 μ g/L (absolute iron deficiency) or serum ferritin 100–299 μ g/L with transferrin saturation $< 20\%$ (functional iron deficiency).⁷⁹³

High-dose oral iron supplementation was evaluated in the IRONOUT trial in patients with HFrEF and did not improve functional capacity; therefore, current evidence does not support its recommendation in patients with HF.⁷⁹⁷

Table 10.2 – Recommendations for the assessment of frailty in patients with heart failure

Recommendation	Strength of recommendation	Certainty of evidence
In patients with HF, we recommend IN FAVOR OF assessment for cachexia, sarcopenia, and frailty as part of prognostic evaluation.	STRONG	HIGH

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Two RCTs evaluated intravenous iron replacement in patients recently hospitalized for DHF. The AFFIRM-AHF trial used ferric carboxymaltose and did not demonstrate a significant reduction in its primary composite outcome of total HF hospitalizations and cardiovascular death at 1 year. However, in its secondary outcomes, there was a 26% reduction in HF hospitalizations (95% CI, 0.58–0.94).⁵³² The IRONMAN trial evaluated ferric derisomaltose using the same primary outcome as AFFIRM-AHF and reported similar findings. However, because the trial was conducted during the COVID-19 pandemic, a prespecified analysis excluding COVID-19-related deaths demonstrated a reduction in the primary outcome at 1 year (rate ratio, 0.76; 95% CI, 0.58–1.00), primarily driven by a reduction in HF hospitalizations (rate ratio, 0.66; 95% CI, 0.46–0.94).⁵³³

Subsequently, the HEART-FID trial evaluated intravenous ferric carboxymaltose in patients with HFrEF and iron deficiency and demonstrated only a modest, nonsignificant reduction in its hierarchical composite outcome of death, HF hospitalization, and functional capacity at 6 months.⁷⁹⁸

Another important study was the FAIR-HF2 trial, which again evaluated ferric carboxymaltose in patients with HF, LVEF < 45%, and iron deficiency. The trial had 3 primary outcomes and was considered positive only if (1) all 3 primary outcomes achieved $p \leq 0.05$, (2) 2 primary outcomes achieved $p \leq 0.025$, or (3) 1 primary outcome achieved $p \leq 0.0167$. The study showed a 21% reduction in the first primary outcome (cardiovascular death or first HF hospitalization; $p = 0.04$), whereas the remaining primary outcomes (HF hospitalization and cardiovascular death or HF hospitalization in patients with transferrin saturation < 20%) did not reach statistical significance. Consequently, the trial was considered negative.⁷⁹⁹

Finally, a 2025 meta-analysis including the 4 trials described above plus the FAIR-HF and CONFIRM-HF trials suggested that patients with HF and iron deficiency experienced a reduction in the composite outcome of cardiovascular death or HF hospitalization at 1 year (RR, 0.72; 95% CI, 0.55–0.89), primarily driven by a reduction in HF hospitalizations (RR, 0.69; 95% CI, 0.48–0.88).⁸⁰⁰

At present, there is no evidence supporting iron supplementation in patients with HFpEF.

Table 10.3 summarizes the recommendations for the evaluation and management of anemia and iron deficiency in patients with HF.

10.6. Renal Dysfunction

CKD and HF share common risk factors and pathophysiological mechanisms beginning in the early stages of disease (stages A and B). As patients progress to stages C and D, the 2 conditions increasingly overlap clinically and exacerbate one another.⁸⁰¹ Thus, several therapies have demonstrated parallel benefits in both renal and cardiovascular outcomes, ACEIs,⁸⁰² ARBs,⁸⁰³ sacubitril-valsartan,⁸⁰⁴ SGLT2 inhibitors,^{805,806} and finerenone.⁷⁶²

In Brazil, the BREATHE registry⁴³³ reported a 24% prevalence of CKD in hospitalized patients with HF.⁸⁰⁷ Recent trials have confirmed the high prevalence of CKD in this population, with rates of 41% in DAPA-HF¹⁴⁶ and 47% in FINEARTS-HF.¹³⁹ No differences in CKD prevalence were observed among patients with HFrEF, HFmrEF, or HFpEF.⁸⁰⁸

CKD is defined as eGFR < 60 mL/min/1.73 m² and/or UACR ≥ 30 mg/g persisting for more than 3 months.⁸⁰⁹ In patients with HF, renal function should preferably be estimated using the 2021 CKD-EPI equation.⁸¹⁰ In HF, the principal mechanism underlying CKD is congestion, by which elevated CVP impairs glomerular hemodynamics, leading to renal hypoperfusion as a secondary phenomenon.⁸⁰¹ Chronic activation of the RAAS and the sympathetic nervous system enhances intrarenal vasoconstriction, sodium and water retention, and fibrosis, establishing a cycle of mutual deterioration. In HFpEF, this process is further aggravated by inflammation and endothelial dysfunction.⁸¹¹

In addition to being an important prognostic marker in HF,⁸¹² impaired renal function often limits the use of RAAS inhibitors because of concerns regarding hyperkalemia and further declines in eGFR.^{801,813} However, these therapies

Table 10.3 – Recommendations for the evaluation and treatment of anemia and iron deficiency in heart failure

Recommendation	Strength of recommendation	Certainty of evidence
In symptomatic patients with HFrEF, we recommend IN FAVOR OF screening for anemia and iron deficiency.	STRONG	HIGH
In symptomatic patients with HFrEF and iron deficiency, we recommend IN FAVOR OF intravenous iron supplementation with ferric carboxymaltose or ferric derisomaltose to relieve HF symptoms and improve quality of life.	STRONG	HIGH
In symptomatic patients with HFrEF and iron deficiency, we recommend IN FAVOR OF intravenous iron supplementation with ferric carboxymaltose or ferric derisomaltose to reduce the risk of HF hospitalization.	WEAK	MODERATE
In patients with HF and anemia, without clinical indications other than HF, we recommend AGAINST the use of erythropoiesis-stimulating agents to improve morbidity or mortality.	STRONG	MODERATE

HF: heart failure; HFrEF: heart failure with reduced ejection fraction.

have been shown to be safe in patients with eGFR as low as 20 mL/min/1.73 m², with benefits comparable to those observed in patients with preserved renal function.^{137,147,804,814} Below this threshold, evidence remains insufficient to support formal recommendations.

Despite the risk of hyperkalemia or declining eGFR, CKD alone is not a contraindication to RAAS inhibitors. Drug discontinuation is justified in the presence of established clinical thresholds, specifically serum creatinine $\geq$ 3.0 mg/dL and/or serum potassium $\geq$ 5.5 mEq/L.⁸⁰¹

During hospitalization for HF, worsening renal function commonly occurs during decongestive therapy. Paradoxically, this transient increase in nitrogenous waste products has not been associated with worse clinical outcomes. In such cases, continuation of RAAS inhibitors is recommended provided that serum creatinine and potassium remain below the thresholds described above.⁸⁰¹ Similarly, in patients with chronic HF, an initial decline in eGFR after initiation of RAAS inhibitors and/or SGLT2 inhibitors has not been associated with poorer prognosis. This early reduction in eGFR is typically transient and is followed by a slower rate of CKD progression, reflecting the long-term nephroprotective effect of these therapies.⁸⁰¹

10.6.1. Prevention of heart failure in patients with chronic kidney disease

Several studies have demonstrated that ACEIs and ARBs,^{815,816} in addition to their nephroprotective effects, are associated with a lower risk of HF-related events. Consequently, these agents are recommended in current CKD and diabetes guidelines.⁸¹⁷ Recently, 2 additional drug classes have been evaluated in this setting: SGLT2 inhibitors and finerenone.

In patients with CKD, the DAPA-CKD⁸¹⁸ and EMPA-KIDNEY⁸¹⁹ trials evaluated SGLT2 inhibitors for the prevention of renal and cardiovascular outcomes. Although both trials enrolled patients with and without diabetes, statistically significant reductions in these outcomes were observed only in patients with type 2 diabetes. In the DAPA-CKD subgroup without diabetes,⁸²⁰ the effect was neutral (HR, 0.84; 95% CI, 0.52–1.36), and, to date, no publication from the EMPA-KIDNEY trial has reported outcomes according to diabetes status. A recent meta-analysis⁷⁵⁹ combining HF and CKD trials demonstrated

similar benefits in patients with and without diabetes. However, when only CKD trials were analyzed, this benefit was no longer observed in patients without diabetes (HR, 0.95; 95% CI, 0.65–1.40). These findings support the use of SGLT2 inhibitors for HF prevention in patients with CKD, type 2 diabetes, and eGFR $>$ 20 mL/min/1.73 m², consistent with the inclusion criteria of the major clinical trials.

In addition, finerenone, a selective nonsteroidal MRA, has demonstrated reductions in both cardiovascular and renal events in patients with CKD and type 2 diabetes. The FIDELIO-DKD^{760,821} and FIGARO-DKD⁷⁶¹ trials, as well as the FIDELITY pooled analysis,⁷⁶² confirmed this cardioprotective effect on the secondary composite outcome of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and HF hospitalization. Therefore, finerenone is also recommended as a preventive strategy in this same clinical setting: CKD + type 2 diabetes + eGFR between 25 and 60 mL/min/1.73 m².

Table 10.4 summarizes the recommendations for the treatment of renal dysfunction in patients with HF.

10.7. Electrolyte Disturbances: Hypokalemia, Hyperkalemia, Hyponatremia, and Hypochloremia

Appropriate management of electrolyte disturbances in HF is essential to prevent serious complications. Hypokalemia and hyperkalemia increase the risk of cardiac arrhythmias, hyponatremia may result in significant neurological complications, and hypochloremia contributes to diuretic resistance. These abnormalities are common throughout the course of HF. Understanding their pathophysiology, actively screening for electrolyte disturbances, and implementing timely interventions have the potential to improve clinical outcomes.

10.7.1. Disorders of Potassium

Fluid and electrolyte disorders are common in patients with HF and have a multifactorial etiology, involving neurohormonal, pharmacologic, and renal factors, all of which adversely affect clinical outcomes.⁸²²⁻⁸²⁴ Hypokalemia and hyperkalemia increase the risk of arrhythmias, hospitalization, and death.⁸²⁵⁻⁸²⁹ The lowest mortality risk is observed in patients with serum potassium levels of 4.0–5.0 mmol/L⁸ (U-shaped relationship).

Table 10.4 – Recommendations for the treatment of renal dysfunction in heart failure

Recommendation	Strength of recommendation	Certainty of evidence
In patients with CKD, type 2 diabetes, and eGFR between 20 and 60 mL/min/1.73 m ² , we recommend IN FAVOR OF the use of SGLT2 inhibitors (dapagliflozin or empagliflozin) to reduce the risk of HF hospitalization, cardiovascular death, and progression of renal dysfunction.	STRONG	HIGH
In patients with CKD, type 2 diabetes, and eGFR between 25 and 60 mL/min/1.73 m ² , we recommend IN FAVOR OF the use of finerenone to reduce HF hospitalizations.	STRONG	MODERATE

HF: heart failure; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; SGLT2: sodium–glucose cotransporter 2.

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10.7.2. Hypokalemia (< 3.5 mmol/L)

Hypokalemia affects up to 50% of patients with HF, particularly those receiving loop diuretics or thiazide diuretics.⁸²⁷ It is associated with an increased risk of ventricular arrhythmias, digitalis toxicity, and death.⁸³⁰ Treatment is guided by the severity of the potassium deficit:

- Mild to moderate hypokalemia (3.0–3.5 mmol/L): oral potassium supplementation, adjustment of diuretic therapy, and initiation or up-titration of a MRA may prevent recurrence.⁸³¹
- Severe hypokalemia (< 3.0 mmol/L): intravenous potassium replacement.

10.7.3. Hyperkalemia (> 5.0 mmol/L)

The incidence of hyperkalemia is approximately 10% to 25% in outpatients with HF, with higher rates observed in those receiving RAAS inhibitors.^{824,826} Among hospitalized patients, the prevalence is approximately 12%, as reported in the BREATHE registry.⁸³² In addition to limiting the implementation of GDMT for HF,⁸³³ hyperkalemia is associated with an increased risk of cardiac arrhythmias and SCD, with a significant increase in mortality,⁸²⁵ particularly among patients with serum potassium > 5.5 mmol/L and those requiring hospitalization.⁸³²

10.7.3.1. Emergency Management of Hyperkalemia (Severe/Acute)

In the acute setting, rapid stabilization is the priority in patients with serum potassium ≥ 6.0 mmol/L, particularly when accompanied by ECG abnormalities (such as peaked T waves or QRS widening) or neuromuscular symptoms. The recommended management strategy includes:⁸²³

- a) Stabilization of the myocardial membrane: Intravenous calcium gluconate, which stabilizes the myocardium but does not reduce serum potassium.
- b) Intracellular potassium shift: These therapies temporarily lower serum potassium (approximately 1.0–1.5 mmol/L) but do not remove potassium from the body:
 - intravenous insulin with glucose;
 - inhaled beta-agonists, particularly when insulin is contraindicated;
 - intravenous sodium bicarbonate in patients with concomitant metabolic acidosis.
- c) Potassium removal:
 - Intravenous loop diuretics (eg, furosemide);
 - Potassium binders, particularly sodium zirconium cyclosilicate (SZC),⁸³⁴⁻⁸³⁶ which has recently been incorporated into the Brazilian Unified Health System (Sistema Único de Saúde [SUS]) for patients with CKD and severe hyperkalemia.
 - Dialysis, for patients with refractory hyperkalemia, oliguria, or persistent volume overload.

Modern potassium binders, including SZC⁸³⁷ and patiomer,^{838,839} promote safe and effective fecal potassium excretion through ion exchange. Currently, SZC is the

only agent available in Brazil. It has an onset of action of 1 hour, with most patients achieving normokalemia within 4 hours, making it an established treatment option for acute hyperkalemia.

10.7.3.2. Prevention of Non-Emergent (Chronic) Hyperkalemia

The primary objective of chronic hyperkalemia management is to maintain or reintroduce RAAS inhibitor therapy. Basic measures include dietary potassium restriction and discontinuation of medications or supplements that increase serum potassium. Sodium polystyrene sulfonate (Sorcal®) is no longer recommended because of the risk of bowel necrosis.

SZC⁸³⁷ has been evaluated in patients with CKD⁸⁴⁰⁻⁸⁴² and HF,^{838,839,843} and subgroup analyses have suggested potential benefits in patients with chronic HF.⁸⁴⁴ The ongoing OPRA-HF trial⁸⁴⁵ is expected to better define the role of SZC in the long-term management of hyperkalemia.

Chart 10.1 summarizes the management approaches according to serum potassium levels.

Table 10.5 summarizes the recommendations for the use of potassium binders in patients with HF.

10.7.4. Hyponatremia

Hyponatremia (serum sodium < 136 mmol/L) is an independent marker of disease severity and occurs in up to 30% of hospitalized patients with HF.⁸⁴⁶ It has been incorporated into several HF prognostic risk scores⁸⁴⁷⁻⁸⁴⁹ as well as the I NEED HELP mnemonic.⁵⁸⁴ Dysfunction and prognosis worsen with decreasing serum sodium concentration, with serum sodium < 125 mEq/L indicating advanced HF.^{850,851}

Treatment is guided by the severity of sodium deficit and the presence of symptoms:⁸⁵²⁻⁸⁵⁴

- Serum sodium > 126 mmol/L and asymptomatic: fluid restriction (800–1000 mL/day) to achieve a negative fluid balance, with no impact on clinical outcomes.^{331,846}
- Serum sodium < 125 mEq/L or symptomatic (delirium, decreased level of consciousness, seizures): hospitalization for slow correction with intravenous hypertonic saline to avoid osmotic demyelination syndrome.^{855,856}
- Persistent hyponatremia: tolvaptan (vasopressin antagonist) may increase serum sodium but does not reduce mortality or hospitalization, as demonstrated in the EVEREST,⁸⁵⁷ TACTICS-HF,⁸⁵⁸ and SECRET⁸⁵⁹ trials. Tolvaptan is not currently available in Brazil.

10.7.5. Hypochloremia

Hypochloremia (serum chloride < 96 mmol/L) is an independent predictor of poor prognosis in (chronic and decompensated) HF and may impair the response to diuretic therapy while contributing to acid–base disturbances.⁸⁶⁰ Chloride depletion, resulting from RAAS activation and exacerbated by loop diuretics, promotes contraction alkalosis, characterized by an increase in blood pH and bicarbonate retention during

Chart 10.1 – Management according to serum potassium levels

Serum potassium (mmol/L)	Clinical management	Additional interventions
<3.0	• Mandatory intravenous potassium replacement. • Monitor ECG and the risk of arrhythmias. • Discontinue loop diuretics whenever possible.	• Hospitalization, continuous ECG monitoring, central venous access, slow intravenous potassium infusion, assessment of magnesium levels and metabolic acidosis.
3.0–3.4	• Oral or intravenous potassium replacement (if symptomatic or ECG abnormalities are present). • Reassess diuretic therapy. • Consider increasing MRA dose.	• ECG monitoring, assessment of magnesium levels, correction of metabolic acidosis, MRA and/or other potassium-sparing agents.
3.5–5.0	• Target range. • Up-titrate RAAS inhibitor and MRA therapy if tolerated.	• Normal-potassium diet. • Adjust diuretic therapy.
5.1–5.4	• Continue RAAS inhibitors with close monitoring. Reinforce a low-potassium diet. • Consider initiating potassium binders if potassium levels continue to rise.	• Low-potassium diet. • Initiate potassium binders. • Assess renal function.
5.5–5.9	• Reduce the dose of or temporarily discontinue RAAS inhibitors and/or MRAs. • Initiate a potassium binder (patiomer preferred).	• Potassium binders, loop diuretics, and sodium bicarbonate if metabolic acidosis is present.
≥6.0	• Severe hyperkalemia requiring urgent stabilization. Discontinue RAAS inhibitors and MRAs. • Consider dialysis. • SZC may be useful in the acute setting.	• Intravenous insulin with glucose, inhaled beta-agonists, intravenous calcium gluconate, and dialysis.

MRA: mineralocorticoid receptor antagonist; ECG: electrocardiogram; RAAS: renin-angiotensin-aldosterone system; SZC: sodium zirconium cyclosilicate.

Table 10.5 – Recommendations for the use of potassium binders in heart failure

Recommendation	Strength of recommendation	Certainty of evidence
In patients with HF and severe hyperkalemia requiring emergency treatment, we recommend IN FAVOR OF the use of a potassium binder (sodium zirconium cyclosilicate) for rapid reduction of serum potassium levels.	STRONG	MODERATE
In patients with HF and chronic hyperkalemia in the outpatient setting, we recommend IN FAVOR OF the use of a potassium binder (sodium zirconium cyclosilicate) to control serum potassium levels and allow the continuation/up-titration of RAAS inhibitor therapy.	WEAK	LOW

HF: heart failure; RAAS: renin-angiotensin-aldosterone system.

extracellular volume contraction. This process reduces urinary excretion of bicarbonate, promotes diuretic resistance at the nephron level, and contributes to refractory congestion.^{861,862}

The recent ADVOR trial⁴³⁰ demonstrated that interventions aimed at correcting hyponatremia, such as the adjunctive use of acetazolamide, may facilitate decongestion, prevent further declines in serum chloride, and enhance the response to diuretic therapy, without serious adverse events.

10.8. Pulmonary Disease and Sleep-Disordered Breathing

COPD is a common comorbidity, affecting approximately 20% of patients with HF, and has a substantial impact on symptoms and clinical outcomes.⁸⁶³⁻⁸⁶⁷ In the OPTIMIZE-HF registry, COPD was identified in 25% of patients, who had a more comorbidities and were less likely to receive beta-blockers or ACEIs during hospitalization.⁸⁶³ COPD is an independent predictor of mortality and hospitalization

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in patients with HF. An analysis of the GISSI-HF trial, which included 6975 participants, demonstrated that COPD was associated with increased all-cause mortality (HR, 1.28; 95% CI, 1.15–1.43; $p < 0.0001$) and the composite outcome of all-cause mortality or cardiovascular hospitalization (HR, 1.19; 95% CI, 1.10–1.30; $p < 0.0001$).⁸⁶⁷

In patients with HF and COPD, beta-blocker therapy is associated with reduced cardiovascular events and improved clinical outcomes. A study including 1573 patients demonstrated reductions in both all-cause and cardiovascular mortality.⁸⁶⁸ The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommends the use of beta-blockers in this population, with a preference for cardioselective beta-blockers.⁸⁶⁹

Evidence regarding the treatment of asthma in patients with HF is more limited. Cardioselective beta-blockers are not an absolute contraindication and may be considered in selected patients, provided that therapy is initiated under close clinical supervision.⁸⁷⁰

Sleep-disordered breathing occurs in more than one-third of patients with HF and is even more prevalent among those with DHF. The most common forms are central sleep apnea (similar to Cheyne–Stokes respiration), obstructive sleep apnea, and a mixed pattern. Both forms are associated with a worse prognosis in HF, although obstructive sleep apnea is the more prevalent form.^{871,872}

In patients with obstructive sleep apnea, nocturnal hypoxemia may be treated with nocturnal supplemental oxygen, continuous positive airway pressure, bilevel positive airway pressure, or adaptive servo-ventilation. However, none of these interventions has demonstrated improvements in clinical outcomes in patients with HF.⁸⁷²

Adaptive servo-ventilation has been associated with increased mortality in 2 RCTs involving patients with HFrEF and central sleep apnea.^{873,874} These findings have subsequently been confirmed by meta-analyses.^{875,876} Therefore, current evidence does not support the use of adaptive servo-ventilation for the treatment of central sleep apnea in patients with HFrEF.^{877,878}

Table 10.6 summarizes the recommendations for the treatment of central sleep apnea in patients with HF.

10.9. Dyslipidemia and Lipid-Lowering Therapy

Lipid-lowering therapies (LLTs) – including statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors – have well-established benefits in ischemic heart disease for both primary and secondary

prevention.⁸⁷⁹⁻⁸⁸² In these settings, the presence of HF does not alter their indication, as major RCTs have consistently demonstrated reductions in cardiovascular events regardless of ventricular function.

Among available LLTs, statins remain the most firmly established therapy in patients with HF, provided there is a formal indication for their use. However, their clinical benefits are observed in the medium and long term. Therefore, in patients with advanced HF and limited life expectancy, discontinuation of statin therapy might be considered, particularly when prescribed for primary prevention.

In contrast, the certainty of evidence supporting other LLTs varies according to the therapeutic class and the clinical profile of patients with HF. Studies evaluating PCSK9 inhibitors, including the FOURIER,⁸⁸³ ODYSSEY OUTCOMES,⁸⁸⁴ and ORION⁸⁸⁵ trials, excluded patients with advanced HF (NYHA class III or IV, or LVEF $< 30\%$ in FOURIER⁸⁸³), thereby limiting the generalizability of their findings to this population. Similarly, icosapent ethyl (REDUCE-IT⁸⁸⁶) and bempedoic acid (CLEAR Outcomes⁸⁸⁷) were not evaluated in patients with advanced HF (NYHA class IV). Therefore, current evidence is insufficient to recommend the routine use of these drug classes in advanced HF.

In nonischemic HF, routine prescription of LLTs is not indicated, as studies have failed to demonstrate reductions in cardiovascular outcomes in patients with nonischemic HFrEF.⁸⁸⁰⁻⁸⁹⁰ Therefore, in the absence of established CAD, LLT should follow the cardiovascular risk stratification and lipid targets recommended by disease-specific prevention guidelines,⁸⁹¹ irrespective of LVEF.

In HFpEF, there is a plausible pathophysiological rationale for the use of statins, based on their potential effects on endothelial dysfunction, inflammation, and metabolic comorbidities.^{892,893} However, the available evidence is limited to observational registry data, such as the JASPER study.⁸⁹⁴ Therefore, until RCTs become available, no formal recommendation can be made.

In summary, LLTs are indicated for secondary prevention in ischemic HF. In nonischemic HF, their prescription should follow recommendations from prevention guidelines. In HFpEF, robust evidence supporting disease-specific use of LLT is currently lacking.

10.10. Hyperuricemia

Hyperuricemia may promote inflammatory activation, oxidative stress, and endothelial dysfunction.⁸⁹⁵ An analysis of the Framingham Heart Study did not support a causal role for serum uric acid in the development of CAD, cardiovascular

Table 10.6 – Recommendations for the treatment of central sleep apnea in patients with heart failure

Recommendation	Strength of recommendation	Certainty of evidence
In patients with heart failure with reduced ejection fraction and predominantly central sleep apnea, we recommend AGAINST the use of adaptive servo-ventilation because of its association with increased all-cause and cardiovascular mortality.	STRONG	MODERATE

mortality, or all-cause mortality; however, it may have a prognostic role.⁸⁹⁶

A meta-analysis demonstrated an association between hyperuricemia and an elevated risk of HF, with a 19% increase in risk for every 1 mg/dL increase in serum uric acid.⁸⁹⁷ Another meta-analysis found an association with all-cause and cardiovascular mortality, where each 1 mg/dL increase in serum uric acid was associated with a 4% increase in the risk of all-cause mortality in patients with HF.⁸⁹⁸

Management of hyperuricemia includes the inhibition of uric acid synthesis (allopurinol, febuxostat) or enhancement of uric acid excretion. The CARES trial compared febuxostat with allopurinol in patients with gout and cardiovascular disease and demonstrated higher all-cause and cardiovascular mortality with febuxostat.⁸⁹⁹ Therefore, allopurinol is the preferred agent for uric acid control.

For the treatment of acute gout flares, nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided because they may worsen renal function and precipitate DHF, increasing the risk by up to 40% in patients with preexisting HF.⁹⁰⁰ Colchicine may represent a safer and better-tolerated alternative in patients with cardiovascular disease.⁹⁰¹

Arthritis is present in up to 43.5% of patients with HF aged ≥ 65 years.¹¹ Rheumatoid arthritis is associated with an approximately 2-fold increase in the risk of developing HF.⁹⁰² The safety of disease-modifying antirheumatic drugs in patients with HF has not been fully established. Moreover, RCTs evaluating TNF inhibitors have demonstrated an increased risk of worsening HF in patients with NYHA class III or IV HF.⁹⁰³

10.11. Erectile Dysfunction

Erectile dysfunction is defined as the persistent inability to achieve and maintain an erection sufficient for satisfactory sexual performance.⁹⁰⁴ HF and erectile dysfunction share several underlying pathophysiological mechanisms, resulting in a prevalence exceeding 80%.⁹⁰⁵ Although its clinical importance is well recognized, erectile dysfunction may remain underrecognized and insufficiently addressed during routine clinical visits.⁹⁰⁶

The management of erectile dysfunction involves 4 actions:⁹⁰⁵ (1) optimal medical therapy for HF; (2) promotion of healthy lifestyle habits; (3) pharmacologic treatment, including PDE5 inhibitors and testosterone replacement therapy in patients with hypogonadism;⁹⁰⁷ and (4) psychotherapy and behavioral therapy.

10.12. Depression

Depression affects up to one-third of patients with HF and is associated with worse clinical outcomes.⁹⁰⁸⁻⁹¹¹ Screening for depression may be performed using validated instruments such as the Hamilton Depression Rating Scale, Beck Depression Inventory, Patient Health Questionnaire-9, and Cardiac Depression Scale.^{4,11}

Treatment includes both nonpharmacologic and pharmacologic interventions. Among nonpharmacologic approaches, cognitive behavioral therapy and structured exercise programs have shown potential benefits. There is

currently no consensus regarding the optimal pharmacologic treatment for depression in the setting of HF. Although safe, sertraline did not reduce depressive symptoms.⁹¹² Escitalopram did not reduce all-cause mortality or hospitalizations, nor did it produce a significant improvement in depression.⁹¹³ Tricyclic antidepressants should be avoided, as should trazodone and nefazodone. Particular attention should be paid to the potential for drug–drug interactions.⁹¹⁴

10.13. Cancer

Despite substantial improvements in cancer survival, prognosis may still be limited by complications related to anticancer therapy. Cardiovascular toxicity associated with anticancer agents accounts for a significant proportion of severe treatment-related complications, particularly HF.⁹¹⁵ The development of HF in patients with cancer may result from the malignancy itself, anticancer therapy, or preexisting cardiovascular risk factors and cardiovascular disease, which are common in this population.⁹¹⁶ Several definitions of cancer therapy–related cardiotoxicity have been proposed, and the most widely accepted currently includes a decline in LVEF, elevation of biomarkers, impaired GLS, and the development of HF symptoms.⁹¹⁷

LV dysfunction secondary to chemotherapy was initially described with anthracyclines. However, cardiotoxicity has subsequently been recognized across multiple classes of anticancer agents, including anti-HER2 monoclonal antibodies (eg, trastuzumab), tyrosine kinase inhibitors (eg, sunitinib, sorafenib, and dasatinib), proteasome inhibitors (eg, bortezomib), microtubule-targeting agents, antimetabolites, and immune checkpoint inhibitors, among others.

Cardiovascular care for patients scheduled to receive potentially cardiotoxic anticancer therapy should begin before treatment initiation. Cardiovascular risk assessment should be conducted in all patients to identify those at increased risk of developing cardiotoxicity and to establish an appropriate strategy for cardioprotection and surveillance. Several risk assessment tools have been developed for this purpose, including the HFA-ICOS tool,⁹¹⁸ which classifies patients into very high-, high-, medium-, or low-cardiovascular risk categories. Patients should undergo evaluation by a cardiologist before initiating anticancer therapy, receive optimal management of cardiovascular risk factors, and be encouraged to adopt a heart-healthy lifestyle.⁹¹⁸

Primary prevention of anthracycline-induced cardiotoxicity consists of interventions implemented before the initiation of anticancer treatment. These strategies include (1) reduction of the cardiotoxic potential of the anticancer regimen, through lower cumulative anthracycline doses, liposomal formulations, continuous infusion protocols, or the use of less cardiotoxic analogs, and (2) administration of cardioprotective therapies.⁹¹⁹ Several pharmacologic strategies have been evaluated for the primary prevention of cardiotoxicity. Dexrazoxane, an iron chelator, is the only cardioprotective agent approved by regulatory agencies for the prevention of cardiotoxicity in high-risk patients, with

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robust evidence demonstrating a reduction in the incidence of HF and cardiac events.⁹²⁰ Regarding cardiovascular medications, evidence from clinical trials is emerging; however, there is currently no established recommendation supporting the routine prophylactic use of ACEIs, beta-blockers, statins, or SGLT2 inhibitors for primary prevention of cardiotoxicity.^{11,917}

The PRADA trial evaluated candesartan and metoprolol succinate for the primary prevention of anthracycline-induced cardiotoxicity, with or without concomitant trastuzumab therapy. The study demonstrated that candesartan provided protection against the decline in LVEF at 6 months.⁹²¹ However, this benefit was no longer evident after 2 years,⁹²² whereas metoprolol showed no protective effect in either the short or long term.

The CECCY trial evaluated carvedilol in a similar clinical setting but excluded patients receiving trastuzumab and did not demonstrate a protective effect on LV function. Nevertheless, carvedilol was associated with potential cardioprotective effects, including lower troponin concentrations, reduced incidence of diastolic dysfunction, and a trend toward less ventricular remodeling, suggesting attenuation of myocardial injury.⁹²³ More recently, the STOP-CA trial randomly assigned 300 patients receiving anthracycline-based chemotherapy to atorvastatin or placebo and demonstrated that atorvastatin reduced the incidence of cardiac dysfunction.⁹²⁴

SGLT2 inhibitors have also been investigated in the field of cardio-oncology. Although current evidence is limited to retrospective studies, available data suggest a potential benefit in preventing LV dysfunction and cardiovascular events. Results from ongoing RCTs are awaited.^{924,925} A recent meta-analysis demonstrated that the use of RAAS inhibitors and beta-blockers for the prevention of anthracycline-induced cardiotoxicity was associated with

a less pronounced reduction in LVEF, higher final LVEF, and a lower incidence of HF, although no changes in mortality were observed.⁹²⁶

Patients who develop elevated troponin concentrations during chemotherapy are believed to be at increased risk of developing cardiotoxicity. Cardinale et al. evaluated enalapril for cardioprotection in 114 patients who developed positive troponin during treatment with high-dose anthracyclines. Compared with placebo, patients randomly assigned to enalapril experienced significantly fewer cardiac events, including HF and asymptomatic LV dysfunction.^{918,927} Another study compared 2 strategies: enalapril in all patients initiated before chemotherapy vs. enalapril initiated only in patients with an increase in troponin during or after chemotherapy. Neither strategy resulted in a significant effect on troponin concentrations.⁹²⁸

The management of HF in patients undergoing anticancer therapy should follow current HF guidelines. When LVEF declines to < 40%, chemotherapy should be interrupted, HF treatment should be initiated, and a discussion with the oncology team is encouraged to determine whether chemotherapy or immunotherapy should be resumed or modified.⁹²⁹ An indication for MCS or heart transplant might also be considered in selected patients. These decisions should be made in close collaboration with the oncology team, taking into account the patient's oncologic status, overall prognosis, and individual preferences.⁶⁴⁶ Dedicated cardio-oncology guidelines are available and provide detailed recommendations for the assessment, surveillance, prevention, and management of cancer therapy-related cardiotoxicity.^{646,917,929}

Table 10.7 summarizes the recommendations for the treatment of HF and prevention of myocardial dysfunction in patients with cancer.

Table 10.7 – Recommendations for the treatment of heart failure and prevention of myocardial dysfunction in patients with cancer

Recommendation	Strength of recommendation	Certainty of evidence
Before initiation of potentially cardiotoxic anticancer therapy, we recommend IN FAVOR OF cardiovascular risk stratification.	STRONG	MODERATE
In patients at moderate or high risk for cardiotoxicity, we recommend IN FAVOR OF evaluation by a cardiologist or cardio-oncologist.	STRONG	LOW
In all patients undergoing anticancer therapy, we recommend IN FAVOR OF cardiovascular risk factor control and physical activity.	STRONG	MODERATE
In patients at high risk for anthracycline-induced cardiotoxicity, we recommend IN FAVOR OF the use of dexrazoxane to prevent the development of myocardial dysfunction.	STRONG	HIGH
In patients at high risk for cardiotoxicity receiving anthracyclines, anti-HER2 therapies, or other anticancer therapies with the potential to cause HF, we recommend IN FAVOR OF the use of ACEIs, beta-blockers, and statins for the primary prevention of cardiotoxicity.	WEAK	HIGH
In patients with HF secondary to cancer therapy-related cardiotoxicity, we recommend IN FAVOR OF management according to current HF guidelines.	STRONG	HIGH

HF: heart failure; ACEI: angiotensin-converting enzyme inhibitor.

10.14. Infections – Influenza and COVID-19

10.14.1. Prevention and Treatment of Influenza Infection

Patients with HF are considered at high risk for cardiovascular events and influenza-related complications. Two meta-analyses^{930,931} evaluated the effects of oseltamivir in high-risk populations, including patients with chronic heart disease and HF. A meta-analysis of 74 observational studies involving high-risk patients found that oseltamivir may reduce mortality (OR, 0.23; 95% CI, 0.13–0.43), hospitalization (OR, 0.75; 95% CI, 0.66–0.89), and duration of symptoms (33 hours; 95% CI, 21–45 hours) compared with no antiviral treatment.⁹³⁰ The analysis also demonstrated that earlier initiation of antiviral therapy was associated with greater clinical benefit.

Another meta-analysis⁹³¹ included RCTs conducted in the general population and analyzed data from 23 studies evaluating oseltamivir, which did not reduce the risk of hospitalization (RR, 0.92; 95% CI, 0.57–1.50). Because no influenza-related deaths occurred in these trials, the population in this analysis is considered low-risk.

10.14.2. Prevention and treatment of COVID-19

Among patients with COVID-19, those with HF experience longer hospital stays, a higher likelihood of requiring mechanical ventilation, and greater mortality than patients without HF.^{932,933} Nirmatrelvir/ritonavir (Paxlovid) has demonstrated efficacy in reducing mortality among patients with COVID-19 who are at high risk for complications, including those with underlying cardiovascular disease. In a cohort study, Paxlovid was associated with reduced mortality among patients with HF who developed COVID-19 (HR, 1.70; 95% CI, 1.47–1.97; $p < 0.001$).^{934,935}

Table 10.8. summarizes the recommendations for the treatment of viral infections (influenza and COVID-19) in patients with HF.

Table 10.8 – Recommendations for the treatment of viral infections (influenza and COVID-2019) in patients with heart failure

Recommendation	Strength of recommendation	Certainty of evidence
In patients with HF and confirmed influenza, we recommend IN FAVOR OF treatment with oseltamivir initiated within 48 hours of symptom onset to reduce symptom duration and hospitalization.	WEAK	LOW
In patients with HF and COVID-19, we recommend IN FAVOR OF treatment with nirmatrelvir/ritonavir (Paxlovid) to reduce disease severity and mortality related to complications.	WEAK	LOW

11. Special Conditions

11.1. Heart Failure During Pregnancy and Postpartum

HF is the leading cause of maternal death during pregnancy and the postpartum period among women with preexisting heart disease.⁹³⁶⁻⁹³⁸ Multicenter studies estimate a global incidence of 112 cases of HF per 100,000 pregnancy-related hospitalizations⁹³⁹ and indicate that 60% of postpartum hospitalizations are attributable to HF. These findings underscore the impact of the postpartum period – often underestimated – on the risk of maternal morbidity and mortality.

The reduced cardiovascular reserve associated with HF limits the ability to adapt to the physiological hemodynamic changes of pregnancy and the postpartum period, including decreased systemic vascular resistance, increased plasma volume, and the progressive increase in cardiac output.⁹⁴⁰

Pregnancy management, delivery planning, and follow-up during the third trimester and postpartum period should be supervised by a multidisciplinary team. Vaginal delivery is generally safe and is the preferred mode of delivery unless contraindicated by obstetric or cardiac conditions. Cesarean delivery should be reserved for obstetric indications, hemodynamic instability, or severe HFrEF. Vaginal delivery should include adequate analgesia and specialized obstetric support during the second stage of labor to control hemodynamic overload, blood loss, and the risk of infection.⁹⁴¹

11.1.1. Pregnancy in Patients with Preexisting Heart Failure

Cardiomyopathies are associated with a 7-fold higher risk of adverse cardiovascular events and a 4-fold higher in-hospital mortality than other forms of cardiovascular disease during pregnancy and the postpartum period.⁹⁴² The cardiomyopathy phenotypes most commonly associated with HF include DCM, HCM, and ARVC.⁹⁴³

LVEF is the primary echocardiographic parameter used to assess LV systolic function.⁹⁴⁴ Both echocardiography and CMR without gadolinium are considered safe during pregnancy, although the diagnostic accuracy of each modality remains limited in certain clinical scenarios.⁹⁴⁵

Reproductive counseling for pregnancy planning should include pregnancy risk stratification according to the modified WHO (mWHO) 2.0 classification.⁹⁴⁶ Women with mild to moderate HFrEF are classified as mWHO class II–III, whereas those with severe HFrEF (LVEF < 30%) or peripartum cardiomyopathy (PPCM) with persistent LV dysfunction are classified as mWHO class IV, in whom pregnancy is formally contraindicated.⁹⁴⁷

Pregnancy after heart transplant should be avoided during the first posttransplant year to ensure stabilization of graft function and immunosuppressive therapy. Contraindications to pregnancy after heart transplant include graft dysfunction, nonadherence to treatment, presence of donor-specific antibodies, significant cardiac allograft vasculopathy, poorly controlled hypertension, diabetes, renal failure,

and active infection. When pregnancy is planned, the immunosuppressive regimen should be adjusted accordingly. Calcineurin inhibitors and corticosteroids are generally considered safe during pregnancy, whereas mycophenolate mofetil and mycophenolic acid are teratogenic.^{948,949}

Pregnancy should be discouraged in women receiving MCS because of the combined risks associated with hemodynamic overload, the teratogenic effects of HF medications, and complications resulting from anticoagulation. In addition, uterine enlargement during pregnancy may compress device components, increasing the risk of RV failure.⁹⁵⁰

Contraceptive counseling for women with HF should be individualized, considering the effectiveness of each contraceptive method, the medical eligibility criteria for contraceptive use,⁹⁵¹ cardiovascular risk, the use of teratogenic medications, complicating factors, and the patient's reproductive goals.⁹⁵² Contraceptives containing ethinyl estradiol should be avoided in women at increased thromboembolic risk. Progestin-only contraceptives, particularly long-acting levonorgestrel contraception, such as subdermal implants and levonorgestrel-releasing intrauterine systems, are recommended because of their superior safety and efficacy in this population.⁹⁵³

In cases of unplanned pregnancy in women with advanced HF classified as mWHO class IV, legal termination of pregnancy may be offered, in accordance with applicable legislation.⁹⁵⁴ Conversely, fertility treatment should be discouraged in women with moderate to severe HFrEF because of the increased risk of complications, including multiple gestation, preeclampsia, and thromboembolic events.⁹⁵⁵

11.1.2. New-Onset Heart Failure During Pregnancy

The diagnosis of HF during pregnancy is challenging because common symptoms such as edema, dyspnea, and fatigue may overlap with the physiological changes of pregnancy. However, the presence of chest pain, persistent cough, orthopnea, paroxysmal nocturnal dyspnea, abnormal BP, tachycardia, or syncope should prompt immediate cardiovascular evaluation. The diagnostic workup should include ECG, echocardiography, chest radiography, and laboratory testing, including measurement of BNP or NT-proBNP, which may assist in the diagnosis of HF during pregnancy.⁴⁶ BNP has demonstrated slightly superior diagnostic accuracy, although studies evaluating NT-proBNP have been limited and have used variable diagnostic thresholds.⁹⁵⁶

11.1.3. Peripartum Cardiomyopathy

PPCM is characterized by HFrEF (LVEF < 45%) with onset toward the end of pregnancy or within the months following delivery, in the absence of another identifiable cause or preexisting heart disease. The main risk factors include preeclampsia, hypertension, multiparity, maternal age > 30 years, multiple gestation, and Black African ethnicity.⁹⁵⁷

The most common presentation of PPCM consists of the typical signs and symptoms of HF, although a small subset of patients may present with CS, complex arrhythmias, or thromboembolic events. Clinical outcomes during the first postpartum year are highly variable, ranging from complete or partial recovery of LV function to adverse outcomes such as death, need for MCS, or heart transplant. In this setting, LVEF is the most reliable predictor of cardiovascular events. Additional factors associated with a worse long-term prognosis include marked LV dilation, RV dysfunction, QT interval prolongation, elevated NP levels, delayed diagnosis, and Black African ethnicity.^{957,958}

As with other familial or hereditary cardiomyopathies, a genetic basis has been proposed for PPCM, supported by the identification of truncating variants in genes such as *TTN*, *FLNC*, *BAG3*, and *DSP*.⁹⁵⁹

11.1.3.1. Special Considerations for the Management of Heart Failure During Pregnancy and Postpartum

The management of HF during pregnancy and the postpartum period follows current HF guidelines, with adaptations aimed at preserving maternal hemodynamic stability while minimizing fetal risk. The discontinuation of potentially teratogenic medications should be carefully weighed against the risk of maternal clinical deterioration.

ACEIs and ARBs are contraindicated during pregnancy because of their well-established adverse fetal effects. During breastfeeding, however, the ACEIs captopril and enalapril might be considered, as they are excreted into breast milk in minimal amounts and are generally well tolerated by nursing infants. Likewise, steroidal MRAs, such as spironolactone, are contraindicated during pregnancy, but their use during breastfeeding may be considered because only negligible amounts are excreted into breast milk.

For nonsteroidal MRAs, such as eplerenone, there are no clinical safety studies; however, experimental data demonstrate fetal and postnatal toxicity, as well as excretion into milk and a contraindication in the package insert.⁹⁶⁰

Among beta-blockers, metoprolol succinate and bisoprolol are preferred for their β_1 -selectivity and favorable safety profile during lactation. Although clinical data remain limited, carvedilol and nitrates have also been widely used in clinical practice.

Hydralazine, digoxin, and diuretics,⁹⁶¹ such as furosemide, are generally considered safe. Anticoagulation should be prescribed according to the patient's thromboembolic risk, particularly in the presence of AF.^{46,942,943,956} Evidence remains insufficient regarding the use of other classes of HF medications, including ARNIs, during pregnancy and lactation. PPCM carries a substantial risk of arrhythmias, with SCD accounting for up to 30% of deaths during the first postpartum year. Risk stratification and indications for antiarrhythmic therapy or an ICD should follow current guideline recommendations.^{957,958}

The use of bromocriptine and cabergoline in PPCM remains controversial, with limited studies and insufficient evidence to recommend their routine use.⁹⁶²

In preclinical studies, SGLT2 inhibitors have been associated with adverse renal effects, fetal growth restriction, and drug transfer into breast milk, with potential impact on neonatal development.⁹⁶² GLP-1 receptor agonists and dual GLP-1/GIP receptor agonists have been associated with fetal growth restriction and skeletal abnormalities in animal studies, without consistent data on lactation. Although an observational study showed no increase in major congenital malformations when these agents were used around conception or during the first

trimester, the number of cases was limited, precluding confirmation of safety.^{963,964}

Given the absence of robust safety evidence and the adverse preclinical findings, the use of SGLT2 inhibitors, GLP-1 receptor agonists, dual GLP-1/GIP receptor agonists, and nonsteroidal MRAs should be contraindicated during pregnancy and lactation.

Table 11.1 summarizes the recommendations for the treatment of patients with HF during pregnancy and the postpartum period.

Table 11.1 – Recommendations for the treatment of patients with heart failure during pregnancy and postpartum

Recommendation	Strength of recommendation	Certainty of evidence
We recommend IN FAVOR OF multidisciplinary care throughout pregnancy and during the first 12 months postpartum.	STRONG	LOW
We recommend IN FAVOR OF vaginal delivery in the absence of obstetric contraindications.	STRONG	LOW
In patients with severe HFrEF or maternal hemodynamic instability, we recommend IN FAVOR OF cesarean delivery.	STRONG	LOW
We recommend IN FAVOR OF transthoracic echocardiography as the preferred and safe imaging modality for evaluating cardiac structure and function during pregnancy.	STRONG	MODERATE
We recommend IN FAVOR OF the use of the mWHO 2.0 risk classification for reproductive counseling and pregnancy planning.	STRONG	LOW
In women classified as mWHO class IV or with a history of PPCM and persistent (moderate to severe) HFrEF, we recommend IN FAVOR OF contraindication to pregnancy.	STRONG	LOW
We recommend IN FAVOR OF individualized contraceptive counseling based on the WHO medical eligibility criteria for contraceptive use.	STRONG	MODERATE
In women with hereditary cardiomyopathy or a positive family history of cardiomyopathy, we recommend IN FAVOR OF pre-pregnancy genetic counseling.	STRONG	MODERATE
We recommend AGAINST the use of ACEIs, ARBs, and aldosterone antagonists during pregnancy.	STRONG	HIGH
The use of ACEIs/ARBs and aldosterone antagonists might be considered during lactation.	WEAK	LOW
We recommend IN FAVOR OF the use of beta-blockers, when indicated, during pregnancy, with dose adjustment according to obstetric and fetal conditions.	STRONG	MODERATE
We recommend AGAINST the use of SGLT2 inhibitors, GLP-1 receptor agonists, dual GLP-1/GIP receptor agonists, and nonsteroidal MRAs during pregnancy.	STRONG	LOW
We recommend AGAINST the use of SGLT2 inhibitors, GLP-1 receptor agonists, dual GLP-1/GIP receptor agonists, and nonsteroidal MRAs during lactation.	STRONG	LOW
In patients with permanent AF or high-risk conditions for thromboembolism, we recommend IN FAVOR OF the use of anticoagulants (enoxaparin* or warfarin).	STRONG	LOW
We recommend IN FAVOR OF long-acting reversible contraception (subdermal implant and LNG-IUS) for their efficacy, safety, and tolerability.	STRONG	LOW
We recommend IN FAVOR OF the use of diuretics (furosemide) during pregnancy and the postpartum period for the management of HF, contingent upon immediate maternal benefit.	STRONG	MODERATE

*Conditional recommendations indicate that the intervention should be considered when the standard alternative is not feasible or when a specific clinical benefit is anticipated. mWHO 2.0: modified World Health Organization classification (version 2.0); AF: atrial fibrillation; LNG-IUS, levonorgestrel-releasing intrauterine system; HFrEF, heart failure with reduced ejection fraction; PPCM: peripartum cardiomyopathy; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; MRA: mineralocorticoid receptor antagonist; SGLT2: sodium-glucose cotransporter 2 (dapagliflozin and empagliflozin); GLP-1: glucagon-like peptide-1.

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11.2. Specific Considerations for the Management of Heart Failure in Chagas Disease

Patients with HF secondary to Chagas disease exhibit some distinctive clinical features, including a higher prevalence of conduction disturbances, RV involvement, autonomic dysfunction, ventricular arrhythmias, and more extensive myocardial inflammation and fibrosis. These characteristics may influence both the therapeutic response and the adverse-effect profile of standard HFrEF therapies compared with patients with other causes of HF. However, despite these particularities, the recommended management of chronic Chagas cardiomyopathy is generally consistent with that of HFrEF of other etiologies and has recently been updated in a dedicated guideline.¹¹³

The following sections summarize the main pharmacologic therapies and cardiac devices used in this population, highlighting their specific considerations in Chagas disease. Because most available evidence supporting pharmacologic and device-based therapies has been generated in patients with HFrEF, the recommendations presented here primarily apply to this phenotype.¹¹³

11.2.1. Diuretics

Diuretics, particularly loop diuretics, are recommended for symptom relief in patients with Chagas-related HFrEF, although no evidence has demonstrated a reduction in mortality. The reduction in preload associated with diuretic therapy requires special attention because RV dysfunction is common in this population.⁹⁶⁵

11.2.2. Digitalis Glycosides

No studies have specifically evaluated the safety or efficacy of digitalis glycosides. Their narrow therapeutic index, together with their potential to exacerbate conduction abnormalities and ventricular arrhythmias, both common features of chronic Chagas cardiomyopathy, requires close clinical monitoring for adverse effects. Despite the lack of evidence of reduced mortality and their potential side effects, digitalis glycosides may be used for symptom control in patients with Chagas-related HFrEF.¹¹³

11.2.3. Beta-blockers

Indirect evidence from robust trials evaluating the efficacy of beta-blockers in patients with HFrEF supports their use. Only a few studies have specifically evaluated beta-blockers in Chagas disease. In the REMADHE trial, a subgroup of 68 patients with Chagas disease demonstrated improved survival, although these patients were not randomly assigned to treatment.⁹⁶⁶ More recently, an observational study including 215 patients with Chagas cardiomyopathy found that beta-blocker therapy was independently associated with reduced mortality.⁹⁶⁷ However, clinicians should remain vigilant for potential adverse effects of beta-blockers, such as conduction disturbances, marked bradycardia, and hypotension, which are common in this population and require close monitoring.

11.2.4. Mineralocorticoid Receptor Antagonists

Evidence from RCTs in patients with HFrEF supports the use of MRAs, such as spironolactone, although no studies have specifically evaluated these agents in this group of patients.¹¹³

11.2.5. Renin–Angiotensin–Aldosterone System Inhibitors

ACEIs and ARBs are widely used in the treatment of HFrEF, with evidence demonstrating a reduction in mortality. In patients with Chagas disease, their use is supported indirectly by studies showing favorable secondary outcomes, although no trials have specifically evaluated their effects on mortality in this population. Because hypotension is common in these patients, careful monitoring for this adverse effect is recommended during treatment with ACEIs or ARBs.¹¹³

11.2.6. Sacubitril-Valsartan

The PARADIGM-HF trial demonstrated that sacubitril-valsartan reduced mortality in patients with HFrEF of diverse etiologies, supporting its use in patients with chronic Chagas cardiomyopathy. However, particular attention should be given to its potent hypotensive effect. In a subgroup analysis of 113 patients with Chagas disease enrolled in the PARADIGM-HF trial, sacubitril-valsartan, compared with enalapril, led to a reduction in mortality and HF hospitalization in patients with chronic Chagas cardiomyopathy, but without statistical significance.⁹⁶⁸

The PARACHUTE-HF trial specifically compared sacubitril-valsartan with enalapril in patients with chronic Chagas cardiomyopathy. Although the rates of cardiovascular death and first HF hospitalization were similar between the 2 groups, treatment discontinuation occurred less frequently with sacubitril-valsartan (6.5% vs. 9.5%). The incidence of adverse events was comparable between groups, supporting the safety of sacubitril-valsartan in this patient population.⁹⁶⁹

11.2.7. Sodium–Glucose Cotransporter 2 Inhibitors

SGLT2 inhibitors are the most recent class of medications shown to reduce mortality in patients with HFrEF. Although no studies have specifically evaluated these agents in patients with Chagas disease, their use might be considered based on indirect evidence supporting their benefits.

11.2.8. Implantable Cardioverter-Defibrillator

The role of ICDs in the secondary prevention of SCD in patients with chronic Chagas cardiomyopathy is well established. ICD implantation is strongly recommended in patients with LVEF $\leq 40\%$ who present with sustained ventricular tachycardia and syncope, syncope with inducible sustained monomorphic ventricular tachycardia during EPS, or hemodynamically stable sustained ventricular tachycardia.¹¹³ In addition, ICD implantation is strongly indicated in patients successfully resuscitated from

ventricular fibrillation or documented sustained ventricular tachycardia, as well as in those with hemodynamically unstable sustained ventricular tachycardia. For the primary prevention of SCD in chronic Chagas cardiomyopathy, risk assessment should incorporate the Rassi risk score together with CMR-quantified myocardial fibrosis.¹¹³

The CHAGASICS trial randomly assigned 323 patients with chronic Chagas cardiomyopathy to treatment with amiodarone or ICD implantation. Although ICD therapy did not reduce all-cause mortality, it was associated with lower rates of SCD, pacemaker implantation, and HF hospitalization.⁹⁷⁰ Therefore, the current Brazilian guidelines for Chagas cardiomyopathy assign a weak (conditional) recommendation for primary prevention ICD implantation in patients with nonsustained ventricular tachycardia, syncope or presyncope of probable cardiac origin with hemodynamically unstable sustained ventricular tachycardia induced during EPS, as well as patients with nonsustained ventricular tachycardia in whom sustained ventricular tachycardia is induced during EPS, followed by amiodarone loading and repeat EPS demonstrating induction of hemodynamically unstable sustained ventricular tachycardia.¹¹³

11.2.9. Cardiac Resynchronization Therapy

No RCTs have specifically evaluated CRT in patients with chronic Chagas cardiomyopathy. Therefore, current recommendations are extrapolated from studies involving other HF etiologies. Patients with symptomatic HF, NYHA class II or III, LVEF $\leq 35\%$, sinus rhythm, LBBB morphology, and QRS duration ≥ 150 ms despite optimal GDMT have a strong indication for CRT. However, observational studies have shown that patients with chronic Chagas cardiomyopathy experience significantly lower survival and have a higher proportion of CRT nonresponders than patients with other forms of cardiomyopathy undergoing CRT. Factors associated with an unfavorable response include the presence and extent of myocardial fibrosis, frequent ventricular arrhythmias, TR, and RV dysfunction, all of which may increase the likelihood of CRT nonresponse in chronic Chagas cardiomyopathy.¹¹³

The specific considerations of treatment options for patients with chronic Chagas cardiomyopathy are summarized in Chart 11.1

11.3. Atrial Cardiomyopathy

Atrial cardiomyopathy is defined as structural, functional, or electrophysiologic abnormalities of the atria that have the

Chart 11.1 – Main specific considerations of treatment options for patients with chronic Chagas cardiomyopathy

Treatment option	Specific consideration
Loop diuretics	– No studies specifically conducted in CCC – Caution regarding right ventricular preload reduction
Digitalis glycosides	– No studies specifically conducted in CCC – Caution regarding conduction disturbances and ventricular arrhythmias
Beta-blockers	– Observational study with reduced mortality – Caution regarding conduction disturbances
Mineralocorticoid receptor antagonists	– No studies specifically conducted in CCC – Indication similar to other etiologies
Renin–angiotensin–aldosterone system inhibitors	– No studies specifically conducted in CCC – Caution regarding hypotension
Sacubitril–valsartan	– Study specifically conducted in CCC (PARACHUTE), demonstrated a favorable safety profile, with a lower discontinuation rate and similar rates of adverse effects across the groups.
Sodium–glucose cotransporter 2 inhibitors	– No studies specifically conducted in CCC – Indication similar to other etiologies
Implantable cardioverter-defibrillator	– Study specifically conducted in CCC (CHAGASICS) – Indication similar to other etiologies
Cardiac resynchronization therapy	– No studies specifically conducted in CCC – Higher frequency of nonresponders

CCC: chronic Chagas cardiomyopathy.

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potential to induce clinically significant manifestations.^{971,972} The morpho-functional substrate of atrial cardiomyopathy includes atrial enlargement, fibrosis, impaired diastolic and contractile atrial function, and electrophysiologic abnormalities, which may progress to AF and endothelial dysfunction. Chat 11.2 presents a classification of atrial cardiomyopathy severity. Proposed etiologies include genetic factors, aging, congestive HF, cardiomyopathies, AF, myocarditis, valvular heart disease, hypertension, obstructive sleep apnea, chronic systemic inflammatory diseases, obesity, diabetes, and endocrine disorders such as hypothyroidism and primary hyperaldosteronism.^{972,973}

From a clinical perspective, although AF and its associated thromboembolic complications represent the most important consequences of atrial cardiomyopathy, other implications include functional MR secondary to LA dilation, worsening cardiac dysfunction, and aggravation of HF symptoms. Recent advances in cardiac imaging have enabled the assessment of LA function, facilitating early cardiovascular risk stratification, treatment decision-making, and follow-up.

Complementary tests used to identify and quantify electrical, mechanical, and structural atrial dysfunction include ECG, echocardiography, CMR, electroanatomical mapping, and biomarkers.⁹⁷¹

On the ECG, a P-wave duration >120 ms and a biphasic P-wave morphology in the inferior leads (II, III, and aVF) are associated with LA enlargement. Patients with advanced interatrial block have a higher risk of AF recurrence after catheter ablation.⁹⁷⁴

Another ECG marker of atrial remodeling is P-wave terminal force in lead V1 (PTFV1). The biphasic P wave in lead V1 reflects propagation of electrical activation through the LA. PTFV1 is calculated by multiplying the amplitude of second portion of the P wave by its width. An absolute PTFV1 > 4 mV·ms is considered abnormal and has been associated with decreased LA appendage ejection velocity and an increased risk of AF.⁹⁷⁵ Other ECG parameters, including P-wave dispersion, P-wave voltage, interatrial block, P-wave axis, and F-wave analysis, have also been associated with atrial cardiomyopathy.⁹⁷¹

Atrial cardiomyopathy is an important component of the pathophysiology of HF, and functional parameters of the LA may be more informative than LA size for its characterization. One echocardiographic parameter that can be used to estimate LA pressure in patients with HF is LASr.^{976,977}

CMR provides an additional method for evaluating atrial function and fibrosis in the characterization of atrial cardiomyopathy.⁹⁷⁸ Regions of LGE identified in the atria may represent relatively advanced fibrotic or non-fibrotic lesions. There is a correlation between fibrosis and post-ablation AF recurrence, and a relationship between the extent of LA fibrosis and stroke.^{979,980}

Electroanatomical mapping is widely used during catheter ablation procedures to identify atrial cardiomyopathy. Diffuse voltage reduction in the LA is associated with LA enlargement and other cardiovascular risk factors.⁹⁸¹

Some serum biomarkers have been suggested to define atrial cardiomyopathy, including markers of HF (NPs), necrosis (troponin), inflammation (sT2), and fibrosis (matrix metalloproteinases and tissue inhibitors of metalloproteinases). However, their use remains controversial.⁹⁷¹

The management of atrial cardiomyopathy should focus on controlling underlying risk factors, treating comorbidities, providing anticoagulation, and implementing GDMT for HF. Appropriate management of comorbidities, such as obesity, obstructive sleep apnea, and excessive alcohol consumption, is fundamental to limiting the progression of atrial cardiomyopathy.^{971,982-987}

In patients with AF, evidence indicates that restoration and maintenance of sinus rhythm can reverse atrial cardiomyopathy. In a meta-analysis of 24 studies including 2040 patients, maximum LA volume decreased by 6.5 mL (95% CI, 4.4–8.6 mL) after catheter ablation, regardless of whether AF was paroxysmal or persistent.⁹⁸⁸

Table 11.2 summarizes the recommendations for the diagnosis and management of atrial cardiomyopathy.

Chart 11.2 – Classification of atrial cardiomyopathy severity

Severity class	Description
Mild (subclinical)	Detected by electrophysiologic measurements or cardiac imaging, without overt arrhythmia or significant atrial mechanical dysfunction.
Moderate (clinically manifest)	Presence of significant structural abnormalities or atrial mechanical dysfunction and elevated biomarkers (B-type natriuretic peptide, atrial natriuretic peptide), and/or atrial fibrillation.
Severe (clinically manifest)	Atrial systolic failure (severely reduced left atrial ejection fraction ($\leq 35\%$) associated with markedly impaired atrial contractility (left atrial appendage ejection velocity: ≤ 20 cm/s), and/or extensive interstitial abnormalities ($\geq 35\%$ of the left atrial wall volume) including atrial fibrosis, fatty infiltration, amyloid infiltration, or inflammation; and/or severe left atrial enlargement (left atrial diameter ≥ 5.0 cm or left atrial volume index ≥ 50 mL/m ²); and/or long-standing persistent/permanent atrial fibrillation .

Table 11.2 – Recommendations for the diagnosis and management of atrial cardiomyopathy

Recommendation	Strength of recommendation	Certainty of evidence
In patients with suspected atrial cardiomyopathy, we recommend IN FAVOR OF the use of ECG to assess electrophysiologic abnormalities and echocardiography to evaluate structural and functional atrial abnormalities.	STRONG	MODERATE
In patients with suspected atrial cardiomyopathy, we recommend IN FAVOR OF cardiac magnetic resonance imaging to evaluate structural and functional atrial abnormalities and atrial fibrosis.	WEAK	LOW
In patients with atrial cardiomyopathy, we recommend IN FAVOR OF rhythm-control strategies to maintain sinus rhythm and prevent progression or promote reversal of atrial cardiomyopathy.	STRONG	MODERATE

ECG: electrocardiogram.

12. Palliative Care in Chronic Heart Failure

12.1. General Definitions, Concepts, and Palliative Care Phases

Despite major advances in HF therapy, a substantial proportion of patients progress to stage D HF, often without eligibility for heart transplant or MCS device implantation. The multidisciplinary team should recognize these patients early and initiate palliative care in partnership with the patient and caregivers, progressively expanding supportive interventions as HF advances, as outlined in Chart 12.1.

According to the WHO, palliative care aims to improve the quality of life of patients and their families through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual.⁹⁸⁹ At this stage, priority shifts toward symptom relief, quality of life, and emotional support, rather than interventions primarily intended to improve medium- or long-term clinical outcomes.⁹⁹⁰ Above all, effective

communication among the health care team, the patient, and family members should be maintained throughout the course of care.

The characteristics most commonly observed in patients considered for a palliative care strategy include > 1 hospital admission or episode of decompensation within the previous 6 months, persistent NYHA class IV symptoms, poor quality of life, dependence in most activities of daily living, ineligibility for heart transplant or MCS, cardiac cachexia or low serum albumin levels, or a diagnosis consistent with terminal illness. Common comorbidities at this stage include depression, dementia, renal failure, anemia, and diabetes.

End-of-life care should be considered only after careful reassessment for reversible causes of decompensation and confirmation that potentially beneficial therapies, such as CRT, coronary revascularization, and heart transplant, have been optimized or are no longer appropriate. The key components of palliative care for patients with HF are summarized in Chart 12.2, based on recommendations from several international professional societies. Most of these

Chart 12.1 – Stages of heart failure and corresponding phases of palliative care

	Stages		
	Stage 1: chronic disease	Stage 2: palliative and supportive care	Stage 3: terminal care
Goals	Therapy to prolong survival Monitoring Symptom control	Optimal symptom control Preservation of quality of life	Optimal symptom control Define and document resuscitation preferences
NYHA functional class	I-III	III-IV	IV
Level of care	Outpatient care	Frequent hospital admissions	Inpatient or outpatient care
Health care professionals	HF specialist	Addition of a palliative care team and a primary care professional	Ensure access to specialists and generalists

INHYA: New York Heart Association; HF: heart failure. Source: Adapted from the documento da European Society of Cardiology⁹⁹⁰

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Chart 12.2 – Palliative interventions for patients with heart failure (in addition to optimal guideline-directed medical therapy)

Symptoms	Palliative interventions
Dyspnea and fatigue	Positive inotropic agents, liberal use of furosemide, high-flow oxygen therapy, morphine, benzodiazepines, rehabilitation, and use of an environmental fan.
Cough	Assess for congestion and reassess the use of angiotensin-converting enzyme inhibitors.
Depression	Selective serotonin reuptake inhibitors, avoidance of tricyclic antidepressants, psychotherapy, rehabilitation, behavioral therapy, and emotional support.
Anxiety	Benzodiazepines, psychotherapy, breathing exercises, and relaxation techniques.
Pain	Assess pain using validated pain scales; avoid nonsteroidal anti-inflammatory drugs; consider morphine, psychotherapy, and occupational therapy. If pain is related to an implantable cardioverter-defibrillator, consider device adjustment.
Dizziness	Adjust the doses of antihypertensive medications.
Edema	Home-based continuous diuretic infusion regimens, optimal medical therapy for heart failure, and skin care.
Nausea and vomiting	Consider discontinuing aspirin; consider using prokinetic agents (metoclopramide or ondansetron) and haloperidol; recommend smaller, more frequent meals.
Constipation	Laxatives, liberalization of fluid restriction when feasible, and dietary modifications to promote bowel regularity.
Insomnia	Evaluate and treat concomitant depression, anxiety, nocturia, sleep apnea, and delirium; reinforce sleep hygiene measures.
Delirium	Investigate precipitating clinical causes, such as metabolic disorders, cardiovascular decompensation, infection, or medication-related adverse effects. Minimize anticholinergic drugs. Consider low-dose antipsychotics when delirium poses a risk to the patient or caregiver.

Source: Adapted from recommendations of the Canadian Society of Cardiology e da Heart Failure Society of America.^{991,992}

recommendations rely primarily on expert consensus, as high-quality evidence remains limited.^{991,992}

Discontinuation of medications or therapies intended primarily to improve medium- and long-term survival, but which may produce short-term adverse effects, should be considered. These may include LLTs (statins), osteoporosis treatments, and vitamin supplementation. In recipients of an ICD who are approaching the end of life, ICD deactivation should be discussed with the patient and family whenever this procedure contributes to frequent adverse effects, such as inappropriate shocks. This practice is recognized as ethically appropriate by the Brazilian Federal Board of Medicine.⁹⁹³

Psychological and spiritual support assume particular importance during this phase of care. Addressing patients' spiritual needs may reduce depressive symptoms and improve quality of life.

12.2. Care of Patients with Advanced Heart Failure and Terminally Ill Patients

Once a patient is characterized as being terminally ill, the ethical principle of nonmaleficence takes precedence over beneficence, and patient autonomy and individual preferences become central to treatment decisions. The primary objective is to establish appropriate limits of care

while respecting the rights of the terminally ill patient. The Declaration of Venice was the first document to systematize medical practice in this context.⁹⁹⁴ Decisions regarding the management of critically ill patients are inherently complex and should be individualized. Hospital ethics committees should participate in the decision-making process to ensure ethically sound clinical practice.

The principal terms and clinical approaches relevant to this setting are summarized below.^{995,996}

12.3. Do-Not-Resuscitate Orders

A do-not-resuscitate (DNR) order is a decision made before the occurrence of cardiac arrest, following discussion among the health care team, the patient, and/or family members, not to initiate cardiopulmonary resuscitation. This decision may also be documented in the patient's advance directives.

12.4. Withholding Life-Sustaining Treatment

Withholding life-sustaining treatment refers to the decision not to initiate medical interventions that would otherwise be considered appropriate and potentially beneficial because it is recognized that the patient will die without the proposed therapy. Such interventions are considered medically futile because they are not expected to alter the patient's prognosis.

12.5. Withdrawal of Life-Sustaining Treatment

Withdrawal of life-sustaining treatment refers to the discontinuation of an ongoing therapeutic intervention without replacing it with an equivalent alternative treatment. In this circumstance, it is understood that the patient will die following the change in the therapeutic plan. Withdrawal is considered ethically and medically justified only when the intervention is regarded as medically futile.

12.6. Terms and Definitions Relevant to this Clinical Context

12.6.1. Orthothanasia

Orthothanasia refers to allowing death to occur at its natural time, without either intentionally hastening death or disproportionately prolonging the dying process.

12.6.2. Dysthansia

Dysthansia refers to the prolongation of the dying process through excessive or disproportionate medical interventions that result in prolonged suffering. Also known as therapeutic obstinacy or medical futility, it involves continuing treatments that no longer provide meaningful benefit to a terminally ill patient and merely prolong the process of dying rather than life itself. Dysthansia is considered the opposite of orthothanasia, as it may compromise the patient's dignity, whereas orthothanasia seeks to preserve a dignified death.

12.6.3. Euthanasia

Euthanasia is the deliberate act of painlessly causing a patient's death to relieve suffering. It is characterized by 2 essential elements: intent and the resulting action. When death is intentionally caused through a direct intervention, it is referred to as "active euthanasia," whereas the omission of a therapeutic intervention with the intention of causing death has been termed "passive euthanasia." Brazilian law prohibits euthanasia.

13. Economic Aspects of Heart Failure in Brazil

13.1. Basic Concepts of Cost-Effectiveness

Cost-effectiveness and budget impact analyses play a key role in the development of clinical guidelines, patient care protocols, and decisions regarding the incorporation of technologies. Incorporating health economic evidence into this guideline aligns clinical recommendations with the realities of both public and private health care financing, promoting the sustainability of HF care in Brazil.

Implementation of public health interventions requires an integrated assessment of clinical effectiveness, safety, and economic efficiency (cost-effectiveness) when evaluating new technologies. In the Brazilian public health system (SUS), these analyses are conducted according to the criteria established by the National Committee for Technology Incorporation into the SUS (Comissão Nacional de Incorporação de Tecnologias

no SUS [CONITEC]) and constitute a mandatory component of new technology assessment. Recently, CONITEC adopted a cost-effectiveness threshold of less than 1 times the gross domestic product (GDP) per capita (approximately BRL 55,500 per quality-adjusted life-year [QALY] in 2025) as representing a cost-effective intervention, whereas values greater than 3 times GDP per capita (approximately BRL 171,000 per QALY in 2025) are considered not cost-effective. Values falling between these thresholds are regarded as having intermediate cost-effectiveness. In the private health care sector, the Brazilian National Regulatory Agency for Private Health Insurance and Plans (Agência Nacional de Saúde Suplementar [ANS]) also requires cost-effectiveness and budget impact analyses during the periodic review of the list of covered health care procedures and events. Although the evaluation framework is similar to that used by the SUS, the ANS applies sector-specific parameters, including pricing data and contractual coverage.

Both regulatory agencies have progressively adopted value-based assessment frameworks to promote greater efficiency, equity, and rational allocation of health care resources.

13.2. Macroeconomics of Heart Failure

Most health care expenditures associated with HF are attributable to hospitalizations, emergency department visits, and invasive procedures.^{17,997-999} Furthermore, patients with HFrEF generally incur higher health care costs than those with HFpEF.^{999,1000}

The economic burden of HF in Brazil is substantial. In 2021, expenditures attributable to HF in the SUS were estimated at BRL 22.1 billion. Between 2008 and 2021, more than 3.4 million HF-related hospitalizations occurred in the SUS, accounting for more than one-third of all hospital admissions for cardiovascular conditions.¹⁰⁰¹ Although the absolute number of clinical admissions has declined in recent years, hospitalizations for coronary revascularization, valve replacement, catheter ablation for cardiac arrhythmias, and cardiovascular device implantation have increased, reflecting the growing severity of cases. Indirect costs are also considerable. Approximately 3% of federal social security expenditures are allocated to disability and retirement benefits related to HF, while productivity losses attributable to the disease are estimated to reach BRL 6 billion annually.^{1001,1002}

The cost of treating an individual patient with HF varies according to NYHA functional class. A Brazilian study using the time-driven activity-based costing (TDABC) method reported average management costs of USD 215 for NYHA class I, USD 296 for NYHA class II, and USD 667 for NYHA class III–IV. Laboratory and imaging tests accounted for an increasingly large proportion of total expenditures, representing up to 74% of costs among patients with NYHA class III–IV HF.¹⁰⁰³

The costs of heart transplant have also been evaluated in Brazil. One study estimated an average cost of USD 74,341 per patient, exceeding the reimbursement provided by the SUS by approximately 60%.¹⁰⁰⁴ These findings underscore the substantial economic burden of HF in Brazil, both through direct health care expenditures and its broader impact on the public health system.

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Globally, HF imposes a considerable economic burden and is associated with challenges related to access to care and treatment adherence, particularly because cardiovascular medications account for a substantial proportion of direct health care costs. Therefore, strategies aimed at improving access and adherence to therapies are essential to mitigate the growing economic impact of HF.¹⁰⁰¹

13.3. Cost-Effectiveness Studies in Heart Failure

13.3.1. Pharmacologic Treatment

In the setting of HFrEF, although the efficacy of beta-blockers, ACEIs, and ARBs in reducing cardiovascular outcomes is well established, no economic evaluations specific to the Brazilian setting are currently available for these therapies.

Economic evaluations of ACEIs and ARBs conducted in several countries during the 1990s and early 2000s demonstrated favorable cost-effectiveness. Enalapril, captopril, and ramipril were shown to be economically attractive treatment options for HFrEF. For enalapril, the incremental cost-effectiveness ratio (ICER) was estimated at USD 115 per QALY gained compared with placebo in patients with LVEF $\leq 35\%$.¹⁰⁰⁵ ARBs were subsequently evaluated in a study conducted in the United Kingdom that assessed the cost-effectiveness of valsartan in patients with post-myocardial infarction LV systolic dysfunction, reporting a favorable ICER of GBP 5300 per QALY compared with placebo.¹⁰⁰⁶

Similarly, studies conducted in the United States, Italy, and the United Kingdom evaluated the cost-effectiveness of beta-blockers (carvedilol, metoprolol succinate, bisoprolol, and nebivolol) in patients with HFrEF receiving optimal medical therapy. In one study, metoprolol succinate, compared with placebo in addition to standard therapy, yielded an ICER of USD 4200 per QALY gained.¹⁰⁰⁷ Overall, these analyses demonstrated that beta-blockers are dominant, cost-effective treatment strategies, including among patients aged > 70 years.¹⁰⁰⁸

Beyond the foundational medical therapy for HFrEF, economic evaluations of adjunctive treatments, including the combination of hydralazine and isosorbide mononitrate, digoxin, and intravenous iron, have also been conducted in other countries, with favorable economic results.¹⁰⁰⁸ For ivabradine, indicated for patients with LV dysfunction, NYHA class II–III, sinus rhythm, HR ≥ 70 bpm, and receiving beta-blockers at the maximum tolerated doses, a U.S. economic analysis estimated an ICER of USD 28,318 per QALY gained, classifying ivabradine as an intervention of intermediate value in health care.¹⁰⁰⁹

From the perspective of the Brazilian public health care system, MRAs have been shown to be cost-effective in patients with ischemic and nonischemic HFrEF. Economic analyses of spironolactone, finerenone, and eplerenone have demonstrated that spironolactone and eplerenone are cost-effective treatment options. Expressed in international dollars (Int\$), the estimated costs per QALY gained were Int\$ 7955 for spironolactone and Int\$ 6459 for eplerenone, both below the adopted willingness-to-pay threshold of Int\$

17,589 (equivalent to 1 Brazilian GDP per capita). Sensitivity analyses indicated that spironolactone and eplerenone were cost-effective in 87% and 92% of iterations, respectively.¹⁰¹⁰

Among SGLT2 inhibitors, dapagliflozin is the agent most extensively evaluated in cost-effectiveness studies. In Brazil, dapagliflozin has been shown to be a cost-effective treatment strategy regardless of diabetes status. The addition of dapagliflozin to standard HF therapy was associated with an estimated gain of 0.36 QALYs, with an ICER of USD 4136.08 per QALY gained. Assuming a willingness-to-pay threshold of USD 8000 per QALY gained, the probability that dapagliflozin is cost-effective was estimated at 96.6%.¹⁰¹¹

The economic evaluation of ARNIs was based on a Latin American subgroup of the PARADIGM-HF trial to better reflect the characteristics of the Brazilian population. Compared with standard HFrEF therapy with enalapril, the use of an ARNI was associated with a gain of 0.57 QALYs and an ICER of BRL 25,832.89 per QALY gained, remaining below the adopted willingness-to-pay threshold.¹⁰¹²

In contrast, for HFpEF, no cost-effectiveness analyses of pharmacologic therapies specific to Brazil are currently available. This represents an important area for future research and for informing public health policy.

13.3.2. Nonpharmacologic Treatment

Exercise training supervised by a qualified exercise training professional is recommended for patients with stable HF. In a Brazilian economic evaluation, a cardiac rehabilitation program consisting of exercise sessions 3 times weekly for 3 months, followed by once-weekly sessions for an additional 9 months (totaling 72 sessions during the first year), demonstrated an ICER of Int\$ 26,462 per QALY, indicating favorable cost-effectiveness in the Brazilian health care setting.¹⁰¹³

A 24-week strategy combining regular home visits with scheduled telephone calls, both led by trained nurses, was evaluated in an RCT and was associated with a 27% reduction in the composite outcome of death, emergency department visit, or hospital readmission.³²³ From the perspective of the SUS, this intervention (home visits plus telephone calls) yielded an ICER of BRL 585 per hospital readmission prevented. From the perspective of the private health care sector, the intervention was dominant, resulting in lower costs and fewer hospital readmissions than usual care.¹⁰¹⁴

In patients with severe or advanced HF, VA-ECMO yielded an ICER of Int\$ 37,491 per QALY compared with standard therapy, supporting its classification as a cost-effective intervention. However, these results were particularly sensitive to the cost of hospitalization and survival probability of patients receiving VA-ECMO.¹⁰¹⁵

The use of remote monitoring systems with data transmission from an ICD was compared with conventional in-person device follow-up every 3 to 6 months in patients with HF. Although the effects on mortality and hospitalization remain uncertain, the early detection of cardiac events, inappropriate ICD shocks, and improved device battery longevity supported its incorporation by CONITEC, based on an agreement that implementation would incur no additional cost.¹⁰¹⁶

13.3.3. Cardiac Resynchronization Therapy and Implantable Cardioverter-Defibrillators

Economic evaluation of implantable cardiac devices is challenging because, although these technologies provide substantial clinical benefits across a broad spectrum of patients with HF, their cost-effectiveness varies considerably according to the characteristics of the eligible population. In addition, their nonlinear cost profile, characterized by substantial upfront expenditures associated with device implantation, limits widespread implementation in most health care systems.

For ICDs, economic evaluations conducted from the perspectives of both the SUS and the private health care sector demonstrated that ICD implantation is not very attractive in terms of cost-effectiveness for the primary prevention of ventricular arrhythmias in patients with HF, regardless of etiology. In contrast, these studies found that ICD therapy becomes cost-effective when restricted to patients at higher risk of ventricular arrhythmias, such as those with ischemic HF, and particularly when indicated for secondary prevention.^{1017,1018}

For CRT, an economic evaluation performed from the perspective of the SUS demonstrated that CRT alone is highly cost-effective in patients with HF who meet established clinical criteria for dyssynchrony. Conversely, upgrade from CRT alone to CRT-D was not cost-effective in the overall eligible population, highlighting the importance of careful patient selection based on a sufficiently high risk of ventricular arrhythmias.¹⁰¹⁹ It should be noted that these Brazilian economic evaluations of ICD and CRT were published during the 2010s. Subsequent advances in device technology and GDMT for HF may have influenced the current cost-effectiveness of these interventions through changes in device costs, device longevity, and the baseline cardiovascular risk of contemporary patient populations.

A more recent economic evaluation specifically examined ICD implantation in a subset of patients with

additional risk factors, characterized by the presence of at least 1 of the following risk factors: nonsustained ventricular tachycardia, frequent PVCs, LVEF < 25%, or presyncope/syncope. In this higher-risk population, ICD therapy was found to be cost-effective, with a cost per QALY gained well below commonly accepted willingness-to-pay thresholds.¹⁰²⁰

13.4. The Brazilian Context

Recognition of the importance of cost-effectiveness analyses as a complement to evidence of clinical efficacy has steadily increased in decisions regarding the incorporation of HF technologies in both the public and private health care sectors. Nevertheless, important evidence gaps remain in Brazil. Most interventions with relevant clinical impact show favorable cost-effectiveness, with costs per QALY below the recommended thresholds despite existing budget constraints. However, many of these technologies have been evaluated in only a single economic analysis, limiting the robustness of the available evidence and its applicability across different health care settings.

Another challenge is the frequent reliance on international data for economic modeling, particularly in earlier studies. This practice requires caution, as differences in health care system organization, local disease epidemiology, and treatment adherence can compromise the accuracy of the results.

Despite these limitations, there has been substantial progress in the production of Brazilian health economic evidence, with an increasing number of research groups generating detailed, high-quality local data. Continued investment in these efforts is essential to support more informed decision-making, expand equitable access to the most cost-effective interventions, and ensure the long-term sustainability of the health care system while improving clinical outcomes for patients with HF (Chart 13.1).

Chart 13.1 – Cost-effectiveness of therapies for the management of heart failure reported in the Brazilian and international literature

Therapy	Qualitative cost-effectiveness	Comments
ACEIs	Dominant or ICER < \$10,000/QALY ¹⁰⁰⁷	Treatment with ACEIs in patients with LV dysfunction for whom ARNI therapy is not feasible is of high value.
ARBs	Dominant or ICER < \$10,000/QALY ¹⁰⁰⁷	Treatment with ARBs in patients with HFrEF who are intolerant to ACEIs and for whom ARNI therapy is not feasible is of high value.
Beta-blockers	Dominant or ICER < \$10,000/QALY ¹⁰⁰⁷	Treatment with beta-blockers in patients with HFrEF using carvedilol, metoprolol succinate, bisoprolol, or nebivolol is of high value.
Dapagliflozin	Dominant or ICER < \$10,000/QALY ¹⁰¹⁰	Treatment with dapagliflozin in patients with HFrEF is of high value.

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Digoxin	Dominant or ICER < \$10,000/QALY ¹⁰⁰⁷	Treatment with digoxin in patients with LV dysfunction, NYHA class II–III, receiving optimal GDMT is of high value. It might be considered in patients who are intolerant or have contraindications to beta-blockers.
Hydralazine plus nitrate in Black patients	Dominant or ICER < \$10,000/QALY ¹⁰⁰⁷	Treatment with hydralazine plus nitrate in Black patients with HFrEF is of high value.
Intravenous iron	Dominant or ICER < \$10,000/QALY ¹⁰⁰⁷	Intravenous iron therapy in patients with HFrEF and iron deficiency, regardless of the presence of anemia, is of high value.
MRAs	ICER between \$10,000 and \$50,000/QALY ¹⁰¹⁰	Treatment with spironolactone and eplerenone in patients with LV dysfunction and NYHA class II–IV is of intermediate value.
Ivabradine (HR > 70 bpm)	ICER between \$10,000 and \$50,000/QALY ¹⁰⁰⁹	Treatment with ivabradine in patients with HFrEF, HR > 70 bpm, and NYHA class II–III is of intermediate value. It might be considered in patients who are intolerant or have contraindications to beta-blockers.
Sacubitril-valsartan	ICER between \$10,000 and \$50,000/QALY ¹⁰¹²	Treatment with ARNIs in symptomatic patients with HFrEF receiving optimal GDMT is of intermediate value.
Cardiac rehabilitation	ICER between \$10,000 and \$50,000/QALY ¹⁰¹³	Cardiac rehabilitation for the treatment of patients with stable HFrEF is of intermediate value.
VA-ECMO	ICER between \$10,000 and \$50,000/QALY ¹⁰¹⁵	Although a Brazilian economic evaluation reported a reasonable ICER for VA-ECMO in patients with refractory cardiogenic shock, ¹⁰¹⁵ a recent RCT ⁶¹³ questioned its clinical benefit; therefore, VA-ECMO is currently considered of intermediate value.

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor–neprilysin inhibitor; GDMT: guideline-directed medical therapy; HFrEF: heart failure with reduced ejection fraction; ICER: incremental cost-effectiveness ratio; LV: left ventricular; MRA: mineralocorticoid receptor antagonist; NYHA: New York Heart Association; QALY: quality-adjusted life-year; VA-ECMO: venoarterial extracorporeal membrane oxygenation; \$: U.S. dollars.

14. Integrated Overview of the Stage-Based Therapeutic Approach and Types of Intervention

This chapter summarizes the most strategic recommendations for the clinical management and organization of care in chronic heart failure (HF), Figure 14.1. The proposed framework is designed to guide healthcare professionals through a structured therapeutic pathway based on disease stage and type of intervention, prioritizing therapies according to their prognostic and clinical impact.

Accordingly, this chapter provides a comprehensive overview of HF management organized by disease stage, encompassing prevention during the early stages (Stages A

and B), the increasing complexity of symptomatic HF (Stage C), including its two major phenotypic presentations—heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF)—and culminating in the management of advanced HF (Stage D).

The chapter presents the full spectrum of therapeutic modalities, including pharmacological therapy (foundational and adjunctive treatments), non-pharmacological interventions, and guideline-directed interventional therapies. Our goal is to provide a clear and structured overview of the therapeutic strategies that modify the natural history of HF, based on the most robust and up-to-date scientific evidence.

GUIDELINES FOR THE MANAGEMENT OF CHRONIC HEART FAILURE Stage-Based Therapeutic Approach and Types of Intervention					
Type of Intervention	Stage A Prevention	Stage B Pre-Heart Failure	Stage C – Symptomatic HF		Stage D Advanced HF
			HFrEF	HFpEF	
 Non-pharmacological measures	- Healthy lifestyle with regular physical activity. - Moderate alcohol intake. - Weight loss (10–15% in obesity).	Maintenance of a healthy lifestyle and the interventions from stage A.	- Multidisciplinary management. - Cardiovascular rehabilitation and physical exercise. - Sodium restriction (< 7 g/day). - Vaccination (influenza, RSV, COVID-19, pneumococcal).	- Multidisciplinary management. - Cardiovascular rehabilitation and physical exercise. - Sodium restriction (< 7 g/day). - Vaccination (influenza, RSV, COVID-19, pneumococcal). - Rigorous control of body weight and comorbidities.	- Warning signs for advanced HF ("I NEED HELP"). - Early referral to a specialized advanced HF center. - Specialized multidisciplinary care. - Palliative care according to patient's needs.
 Pharmacological measures	- Control of hypertension (BP < 130/80 mmHg). - DM: SGLT2 inhibitors, GLP-1 receptor agonists, and dual GIP/GLP-1 receptor agonists. - Dyslipidemia: statins. - Management of cardiotoxicity (chemotherapy and AAS).	- ACEI/ARB + BB (post-MI, LVEF ≤ 50%, NICM or Chagas). - MRA (post-MI with LVEF ≤ 40% and/or DM).	Foundational Medical Therapy (FMT): - ARNI / ACEI. - ARB (if ACEI/ARNI not tolerated). - BB. - Non-steroidal MRA. - SGLT2 inhibitor. Additional Medical Therapy (AMT): - Loop diuretics. - Hydralazine + nitrate. - Ivabradine (HR > 70 bpm). - Digoxin. - IV iron.	- SGLT2i inhibitor (first line). - MRA. - GLP-1 receptor agonist and dual GLP-1/GIP receptor agonist (obesity). - Loop diuretics. - Management of comorbidities. (Note: ACEI, ARB, ARNI and BB have no proven benefit and should be considered only in specific clinical scenarios, e.g., comorbidities; BB without proven benefit, with a potential bradycardic effect).	- Optimization of guideline-directed medical therapy (GDMT) as tolerated. - Consider gradual withdrawal of non-beneficial drug classes, with monitoring for adverse effects (hypotension, electrolyte disorders, renal function). - IV diuretics (up-titration of doses). - Sequential nephron blockade.
 Guideline-directed invasive therapy	(Not applicable – focus on primary prevention)	- Treatment of significant valvular disease. - Myocardial revascularization.	Electrical devices: - ICD (primary/secondary prevention). - CRT (biventricular). - Conduction system pacing (bundle branch area pacing). Percutaneous: - M-TEER (mitral edge-to-edge repair). - TAVI (transcatheter aortic valve implantation). - Catheter ablation (AF). Surgical: - Surgical revascularization. - Valvular surgery.	(No specific structural invasive therapy recommended; focus on comorbidity control)	- INTERMACS classification for clinical stratification. - Heart transplantation (definitive). - Long-term mechanical circulatory support (MCS): bridge to transplant or destination therapy. - Short-term mechanical circulatory support (MCS): bridge to transplant or to decision.

Figure 14.1 – General overview of the recommended treatments for HF according to the evolution stages and type of intervention. HF: Heart Failure; HFrEF: Heart Failure with Reduced Ejection Fraction; HFpEF: Heart Failure with Preserved Ejection Fraction; LVEF: Left Ventricular Ejection Fraction; HTN: Hypertension; DM: Diabetes Mellitus; T2DM: Type 2 Diabetes Mellitus; MI: Myocardial Infarction; NICM: Non-Ischemic Cardiomyopathy; AF: Atrial Fibrillation; HR: Heart Rate; AAS: Anabolic-Androgenic Steroids; RSV: Respiratory Syncytial Virus; FMT: Foundational Medical Therapy; AMT: Adjunctive Medical Therapy; GDMT: Guideline-Directed Medical Therapy; ACEI: Angiotensin-Converting Enzyme Inhibitor; ARB: Angiotensin Receptor Blocker; ARNI: Angiotensin Receptor–Neprilysin Inhibitor; BB: Beta-Blocker; MRA: Mineralocorticoid Receptor Antagonist; SGLT2i: Sodium–Glucose Cotransporter 2 Inhibitor; GLP-1 RA: Glucagon-Like Peptide-1 Receptor Agonist; IV: Intravenous; ICD: Implantable Cardioverter-Defibrillator; CRT: Cardiac Resynchronization Therapy; M-TEER: Mitral Transcatheter Edge-to-Edge Repair; TAVI: Transcatheter Aortic Valve Implantation; LVAD: Left Ventricular Assist Device; MCS: Mechanical Circulatory Support; INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support; I NEED HELP: Clinical mnemonic for risk stratification and referral of patients with advanced heart failure.

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