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Review Article

Advancements in the Management of Heart Failure with Reduced Ejection Fraction (HFrEF): Current Strategies and Future Directions

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ABSTRACT

Heart failure with reduced ejection fraction (HFrEF) remains a major clinical challenge, with evolving management strategies aimed at improving patient outcomes. This article provides a comprehensive overview of current treatment protocols for HFrEF, including the role of guideline-directed medical therapy (GDMT), multidisciplinary care teams, and emerging therapies. It outlines the core pharmacological agents recommended in recent guidelines, such as ACE inhibitors/ARNI, beta-blockers, mineralocorticoid receptor antagonists (MRAs), and SGLT2 inhibitors, highlighting their pivotal role in optimizing treatment. The article also addresses the importance of early initiation of these therapies and the need for a personalized, patient-centered approach. Emerging therapies, including novel agents like vericiguat and the increasing use of device-based interventions, such as remote monitoring and implantable devices, are discussed as promising avenues to improve heart failure management. Additionally, the article emphasizes the need for an integrated care model, involving heart failure specialists and a collaborative approach to patient education and support. The future of HFrEF management looks promising, with advancements in pharmacotherapy, precision medicine, and technology. Challenges such as hospitalization prevention, quality of life improvements, and personalized care remain, underscoring the importance of continued research and innovation in managing this complex condition.

Keywords: Heart failure with reduced ejection fraction (HFrEF), Guideline-directed medical therapy (GDMT), ACE inhibitors, SGLT2 inhibitors, Future directions in HFrEF.

INTRODUCTION

Heart failure is a multifaceted syndrome categorized primarily based on left ventricular ejection fraction (LVEF). The classifications include [1]:

- Heart Failure with Reduced Ejection Fraction (HFrEF): LVEF < 40%, characterized by diminished contractility and reduced cardiac output. Common symptoms include fatigue, shortness of breath, and fluid retention.
- Heart Failure with Mildly Reduced Ejection Fraction (HFmrEF): LVEF between 40% and 50%, presenting features of both HFrEF and HFpEF with variable clinical implications.
- Heart Failure with Preserved Ejection Fraction (HFpEF): LVEF > 50%, marked by preserved systolic but impaired diastolic function, often linked to challenges in ventricular filling. This form is particularly complex due to its heterogeneous nature and association with conditions like hypertension and obesity.
- Heart Failure with Improved Ejection Fraction (HFimpEF): Patients with baseline LVEF < 40% showing an improvement of ≥10 percentage points to LVEF > 40%, often in response to effective treatment.

Epidemiology

Heart failure is a leading cause of global morbidity and mortality, affecting over 26 million people worldwide, including 6.2 million adults in the United States. The prevalence rises sharply with age, from 1–2% in individuals aged 40–59 years to 12% in those over 80. At age 55, the lifetime HF risk is 33% for men and 28% for women [2].

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Although hospitalizations for HF peaked at around 1 million per year by 2000, they have declined to 809,000 by 2016 due to improved management and preventive strategies. However, the rising obesity rates globally may reverse these positive trends. The epidemiology of HF also reflects significant racial disparities, with black populations at the highest risk, followed by Hispanic, white, and Chinese Americans [3].

Heart failure remains a serious condition with poor long-term outcomes. Approximately 50% of patients survive five years post-diagnosis, and for those with severe HF, 1-year mortality can reach 40%. In the United States, HF is a factor in 1 in 8 deaths, primarily due to progressive HF or sudden cardiac death [4].

Hospitalizations are frequent, with 83% of patients hospitalized at least once following an HF diagnosis. Subsequent admissions increase mortality risk, with rates ranging from 8–14% at 30 days, 26–37% at 1 year, and up to 75% at 5 years. Readmission rates are also high, varying between 20–50% within six months [4].

Pathophysiology of HFrEF

Heart failure with reduced ejection fraction (HFrEF) progresses over time, beginning with an initial event that triggers structural and functional changes in the heart. This index event may be acute, such as a myocardial infarction, or gradual, as seen in chronic pressure or volume overload, genetic cardiomyopathies, or congenital conditions. Initially, compensatory mechanisms help maintain cardiac function, often delaying the onset of symptoms. However, these adaptations eventually contribute to disease progression as structural and functional deterioration continues [5].

HFrEF is characterized by left ventricular dysfunction, involving extensive remodeling and fibrosis that compromise cardiac performance. Ventricular remodeling includes two types of hypertrophy: concentric hypertrophy, caused by pressure overload (e.g., hypertension), which increases myocardial mass without enlarging the chamber size; and eccentric hypertrophy, driven by volume overload (e.g., valvular regurgitation), which enlarges both chamber volume and myocardial mass. On a cellular level, remodeling features myocyte hypertrophy, increased collagen deposition, disrupted calcium handling, apoptosis, and fetal gene reexpression, all of which impair contractility and relaxation. Additionally, increased wall stress and systemic vasoconstriction result in afterload mismatch, further worsening pump dysfunction and driving adverse remodeling [6].

While the mechanisms of HFrEF involve myocyte loss, hypertrophy, and fibrosis, HFpEF is driven by diastolic dysfunction, often exacerbated by hypertension, vascular stiffness, and metabolic inflammation. In HFpEF, impaired ventricular relaxation, renal dysfunction, sodium retention, and oxidative stress lead to elevated filling pressures and fluid overload, particularly in older patients [7].

Ventricular remodeling in HFrEF involves multiple changes. At the cellular level, abnormalities in excitation-contraction coupling, β-adrenergic receptor desensitization, and myocyte hypertrophy occur alongside impaired cytoskeletal proteins. Changes in myocardial composition, including myocyte necrosis, apoptosis, fibrosis, and matrix degradation, contribute to reduced cardiac function. Geometrical changes, such as ventricular dilation, wall thinning, and papillary muscle displacement, result in atrioventricular valve regurgitation, worsening overall heart performance [8].

Therapeutic approaches for HFrEF primarily focus on improving contractility and reducing afterload, while HFpEF treatments target hypertension, vascular stiffness, and metabolic factors. A deeper understanding of these mechanisms is essential to enhance management strategies and improve outcomes for patients with heart failure.

Neurohormonal Activation in Heart Failure

In response to reduced cardiac output, the sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS) are activated to maintain perfusion. The SNS increases heart rate, contractility, and vascular resistance, stabilizing blood pressure. Concurrently, RAAS activation leads to vasoconstriction via angiotensin II, sodium retention through aldosterone, and fluid volume expansion, temporarily improving preload and cardiac output [9].

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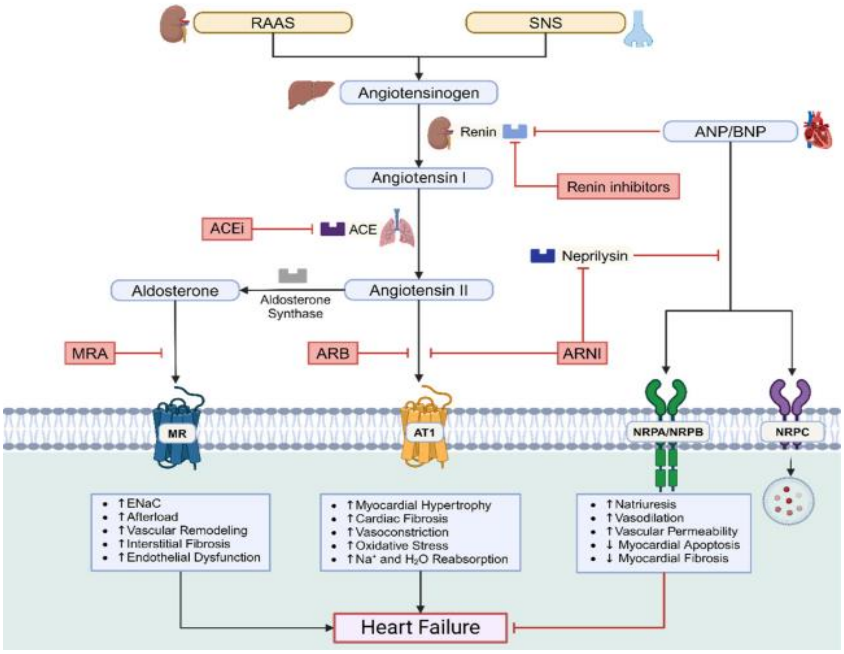

Figure 1: Neurohormonal activation in heart failure.

ACE-I=angiotensin-converting enzyme inhibitor; ANP=atrial natriuretic peptide; ARB=angiotensin receptor blocker; ARNI=angiotensin receptor-neprilysin inhibitor; CRT-D=cardiac resynchronization therapy with defibrillator; RAAS=renin angiotensin aldosterone system; SNS=sympathetic nervous system.

Prolonged neurohormonal activation has detrimental effects. Persistent vasoconstriction increases afterload, reducing pumping efficiency, while sodium and water retention lead to volume overload and symptoms like pulmonary edema. Baroreceptor desensitization disrupts blood pressure regulation, and continuous RAAS and SNS activity induces myocardial toxicity, fibrosis, apoptosis, and arrhythmias (Figure 1). Additionally, these changes drive tissue remodeling in the heart and other organs, exacerbating heart failure progression [10].
Natriuretic peptides like ANP and BNP are released in response to myocardial stretch due to volume overload. They serve as protective mechanisms, inducing vasodilation, promoting sodium and water excretion, and inhibiting RAAS activity. These actions reduce afterload, preload, and fluid retention, alleviating heart failure symptoms [11].

Prostaglandins, bradykinin, nitric oxide, and adrenomedullin act as counter-regulatory agents, inducing vasodilation, enhancing natriuretic peptide effects, and opposing RAAS activation. These hormones improve vascular resistance, diuresis, and overall cardiac function [12].

Endothelin, a potent vasoconstrictor, promotes fibrosis and hypertrophy, worsening heart failure. Similarly, inflammatory cytokines and oxidative stress contribute to cardiac remodeling and functional decline, perpetuating the disease process [12].

Etiologies of Heart Failure

Heart failure with reduced ejection fraction (HFrEF) has diverse causes, with ischemic heart disease as the leading contributor. Hypertension-induced cardiomyopathy is another significant factor, where prolonged pressure overload leads to left ventricular dysfunction. Non-ischemic dilated cardiomyopathy, often linked to genetic or idiopathic factors, also contributes to HFrEF. Toxic exposures, such as excessive alcohol consumption or chemotherapy, and conditions like myocarditis and inflammatory cardiomyopathies, can further lead to myocardial damage and reduced ejection fraction [13].

Heart failure with preserved ejection fraction (HFpEF) arises from multifactorial causes, often associated with comorbidities like hypertension, diabetes, obesity, and coronary artery disease. These conditions induce pathological changes, including left ventricular hypertrophy, myocardial fibrosis, endothelial dysfunction, and systemic inflammation, all of which impair diastolic function and contribute to HFpEF [14].

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Precipitating Factors in Heart Failure

Heart failure may worsen due to excessive physical exertion, emotional stress, or high fluid and sodium intake. Nonadherence to prescribed medications or heavy alcohol consumption are common triggers that exacerbate symptoms.

Certain medications can worsen heart failure, such as nonsteroidal anti-inflammatory drugs (NSAIDs) that promote fluid retention or calcium channel blockers with negative inotropic effects. Failure to recognize congestion or underuse of diuretics can also precipitate decompensation [15].

Uncontrolled hypertension, myocardial ischemia, arrhythmias, or pulmonary embolism can directly destabilize heart failure. These events often require prompt intervention to prevent further decline [16].
Systemic infections, renal or hepatic failure, hyperthyroidism, untreated sleep apnea, and anemia are additional factors that exacerbate heart failure. Addressing these underlying conditions is crucial to stabilizing patients and preventing recurrent decompensation [16].

Clinical Presentation

Heart failure presentswith symptoms such as shortness of breath, reduced exercise tolerance, fatigue, ankle swelling, orthopnea, and paroxysmal nocturnal dyspnea. Key signs include elevated jugular venous pressure, a third heart sound (S3 gallop), laterally displaced apical impulse, pulmonary crepitations, and peripheral edema. Clinical findings like S3 gallop, elevated jugular venous pressure, and peripheral edema are crucial in identifying heart failure.

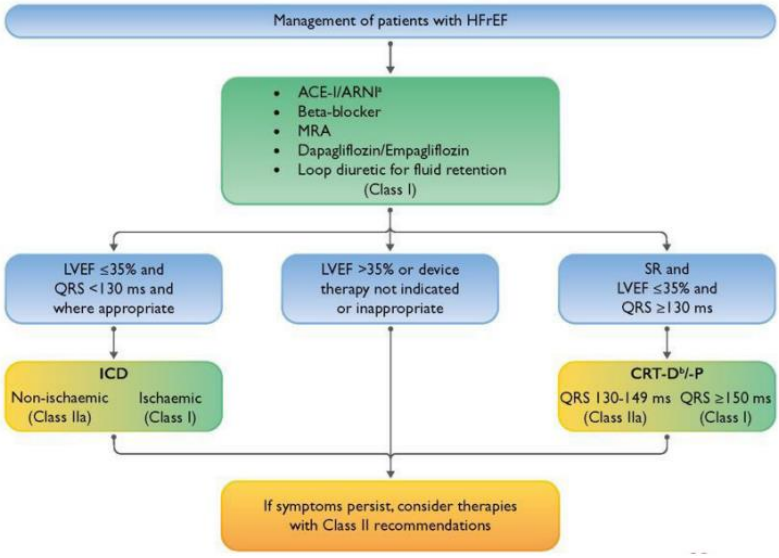

Figure 2: Management of heart failure.

ACE-I=angiotensin-converting enzyme inhibitor; ARNI=angiotensin receptor-neprilysin inhibitor; CRT-D=cardiac resynchronization therapy with defibrillator; CRT-P=cardiac resynchronization therapy pacemaker; ICD=implantable cardioverter-defibrillator; HFrEF=heart failure with reduced ejection fraction; MRA=mineralocorticoid receptor antagonist; QRS=Q, R, and S waves of an ECG; SR=sinus rhythm. aAs a replacement for ACE-I. bWhere appropriate. Class I=green. Class IIa=Yellow.

Echocardiography is the gold standard for measuring ejection fraction and assessing cardiac function. Cardiac MRI provides detailed myocardial assessment and detects fibrosis. Elevated NT-proBNP and troponins aid in diagnosis and risk stratification [17]. Different management strategies for heart failure are illustrated in Figure 2.

Pharmacologic Management

ACE Inhibitors (ACEIs) and ARBs: ACEIs, such as enalapril or lisinopril, reduce mortality and symptoms by inhibiting the renin-angiotensin-aldosterone system (RAAS), decreasing sodium retention, and lowering afterload.ARBs are alternatives for patients intolerant to ACEIs (e.g., those experiencing cough) but may have less robust mortality data [18].

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Beta Blockers: Beta blockers reduce the harmful effects of sympathetic overactivity, lowering heart rate and myocardial oxygen demand while improving survival. Evidence shows a 35% reduction in mortality with beta-blockers in HFrEF [18].

Mineralocorticoid Receptor Antagonists (MRAs): MRAs, including spironolactone and eplerenone, are essential in managing HFrEF by blocking aldosterone's effects, which include sodium retention and myocardial fibrosis. Clinical trials report about a 30% mortality reduction when MRAs are added to ACE inhibitors. Spironolactone, with antiandrogenic properties, may cause side effects like gynecomastia, while eplerenone, being more selective, is better tolerated and particularly effective post-myocardial infarction. MRAs are potassium-sparing diuretics, which help avoid hypokalemia but risk hyperkalemia, especially in patients with renal impairment. Electrolyte monitoring is crucial for safe use [18].

Second-Line Therapies: ARNIs (e.g., sacubitril/valsartan) combine angiotensin receptor blockade with neprilysin inhibition, enhancing natriuretic peptides for vasodilation and improved outcomes. PARADIGM-HF trial demonstrated a 20% reduction in sudden cardiac death compared to ACE inhibitors. SGLT2 inhibitors, initially for diabetes, benefit HFrEF patients by reducing hospitalizations and cardiovascular mortality through mechanisms like natriuresis and improved myocardial energetics. These therapies significantly enhance HFrEF management beyond traditional treatments [18].

Adjunctive Therapies: Loop diuretics are pivotal for fluid overload management but lack mortality benefits. In cases of decompensation, high or intravenous doses may be needed. Thiazide diuretics may help with diuretic resistance, though careful electrolyte monitoring is necessary. Ivabradine aids in heart rate control in specific scenarios, while hydralazine and isosorbide dinitrate are particularly effective in African American patients [18].

Advanced Therapies: Implantable cardioverter-defibrillators (ICDs) prevent sudden cardiac death in patients with LVEF <35% despite optimal therapy. Cardiac resynchronization therapy (CRT) improves symptoms and outcomes in HFrEF with QRS prolongation, delivered as CRT-P (pacing) or CRT-D (pacing and defibrillation). CRT addresses dyssynchrony to enhance cardiac function. Left ventricular assist devices (LVADs) serve as a bridge to transplant or destination therapy, and heart transplantation is reserved for end-stage cases [19].

Table 1: Pharmacological management of heart failure: Initiation and target doses.

	Starting Dose	Target Dose
Beta-blockers		
Bisoprolol	1.25 mg once daily	10 mg once daily
Carvedilol	3.125 mg twice daily	25 mg twice daily for weight <85 kg and 50 mg twice daily for weight ≥85 kg
Metoprolol succinate	12.5-25 mg daily	200 mg daily
ARNI		
Sacubitril/valsartan	24/26 mg to 49/51 mg twice daily	97/103 mg twice daily
ACE inhibitors		
Captopril	6.25 mg 3× daily	50 mg 3× daily
Enalapril	2.5 mg twice daily	10-20 mg twice daily
Lisinopril	2.5-5 mg daily	20-40 mg daily
Ramipril	1.25 mg daily	10 mg daily
ARBs		
Candesartan	4-8 mg daily	32 mg daily
Losartan	25-50 mg daily	150 mg daily
Valsartan	40 mg twice daily	160 mg twice daily
Mineralocorticoid antagonists		
Eplerenone	25 mg daily	50 mg daily
Spironolactone	12.5-25 mg daily	25-50 mg daily
SGLT inhibitors		
Dapagliflozin	10 mg daily	10 mg daily
Empagliflozin	10 mg daily	10 mg daily
Sotagliflozin	200 mg daily	400 mg daily
Vasodilators		
Hydralazine	25 mg 3× daily	75 mg 3× daily
Isosorbide dinitrate†	20 mg 3× daily	40 mg 3× daily
Fixed-dose combination isosorbide dinitrate/hydralazine‡	20 mg/37.5 mg (one tab) 3× daily	2 tabs 3× daily
Ivabradine		
Ivabradine	2.5-5 mg twice daily	Titrate to heart rate 50-60 beats/min. Maximum dose 7.5 mg twice daily
Oral soluble guanylyl cyclase stimulator		
Vericiguat	2.5 mg daily	10 mg daily

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ACC = American College of Cardiology; ACE = angiotensin-converting enzyme; AHA = American Heart Association; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor/neprilysin inhibitor; GDMT = guideline-directed medical therapy; HF = heart failure; HFrEF= heart failure with reduced ejection fraction; HFSA = Heart Failure Society of America; SGLT = sodium-glucose cotransporter; tab = tablet.

Emerging Therapies and Non-Pharmacological Interventions in HFrEF

SGLT2 inhibitors like dapagliflozin and empagliflozin, originally for type II diabetes, now show about a 25% reduction in heart failure worsening or cardiovascular death in HFrEF, regardless of diabetes status. Current guidelines strongly recommend early SGLT2i use. Initial doses vary by drug, with gradual titration to effective levels. However, concurrent use with ARNIs and loop diuretics requires careful monitoring to prevent over-diuresis. Initiating multiple therapies in frail or comorbid patients is challenging, underscoring the need for heart failure nurse specialists to guide and monitor care [20].

Table 2: Indications for ARNI, Ivabradine, SGLT Inhibitor, and Vericiguat Use.

Indications for Use of an ARNI in HFrEF
■ NYHA functional class II-IV HF ■ Administered in conjunction with a background of GDMT for HF in place of an ACE inhibitor or ARB
Indications for Use of Ivabradine in HFrEF
■ LVEF ≤35% ■ On maximum tolerated dose of beta-blocker ■ Sinus rhythm with a resting heart rate ≥70 beats/min ■ NYHA functional class II or III HF
Indications for Use of an SGLT Inhibitor in HFrEF
■ HFrEF (EF ≤40%) with or without diabetes ■ NYHA functional class II-IV HF ■ Administered in conjunction with a background of GDMT for HF
Indications for Use of Vericiguat
■ HFrEF (LVEF <45%) ■ On maximum tolerated GDMT ■ Worsening HF symptoms

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; EF = ejection fraction; GDMT = guidelinedirected medical therapy; HF = heart failure; HFrEF= heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SGLT = sodium-glucose cotransporter.

Emerging treatments include omecamtivmecarbil, gene therapy, and stem cell therapy. Remote monitoring devices like CardioMEMS track pulmonary artery pressure, offering evidence-based adjustments and reducing hospitalizations, particularly in NYHA Class III patients. Despite evolving technologies, robust evidence for clinical benefit is still limited, requiring tailored team-based approaches [21].

Dietary measures, including sodium restriction and fluid management, are critical. Cardiac rehabilitation and exercise training significantly enhance quality of life, clinical outcomes, and exercise capacity but remain underutilized in many regions. Integrated heart failure teams, led by specialist nurses and cardiologists, coordinate care, emphasizing multidisciplinary collaboration with primary care physicians, pharmacists, and dietitians [22].

Educating patients and caregivers on medication adherence, recognizing worsening symptoms, and self-care practices empowers them to actively manage their condition. Comprehensive care through integrated teams, combined with education and expanded access to cardiac rehabilitation, remains essential to improving outcomes for HFrEF patients [22].

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Table 3: Dose Adjustments of Sacubitril/Valsartan for Specific Patient Populations

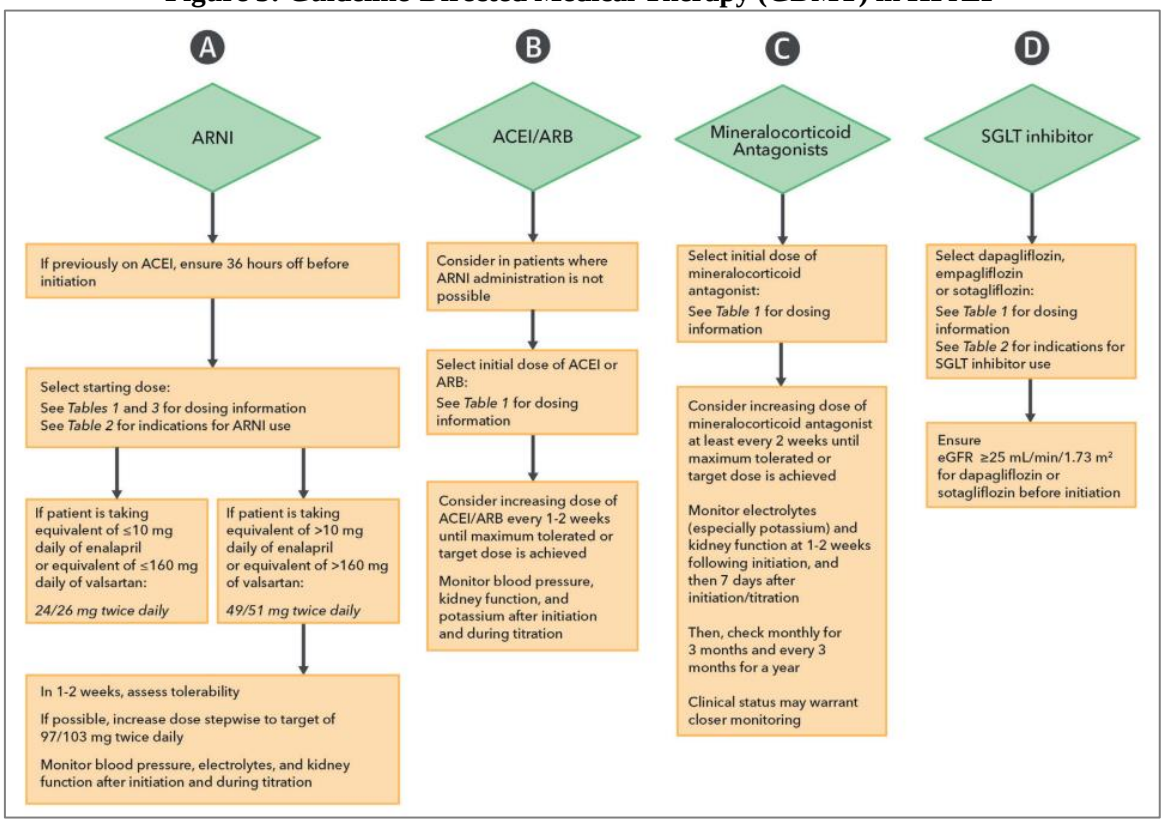
Population	Initial Dose
High-dose ACE inhibitor *>10-mg total daily dose of enalapril or therapeutically equivalent dose of another ACE inhibitor* *High-dose ARB* *>160-mg total daily dose of valsartan or therapeutically equivalent dose of another ARB*	**49/51 mg twice daily**
De novo initiation of ARNI *Low- or medium-dose ACE inhibitor* *≤10-mg total daily dose of enalapril or therapeutically equivalent dose of another ACE inhibitor* *Low- or medium-dose ARB* *≤160-mg total daily dose of valsartan or therapeutically equivalent dose of another ARB*	**24/26 mg twice daily**
ACE inhibitor/ARB-naive	
Severe kidney impairment (eGFR <30 mL/min/1.73 m²)*	
Moderate hepatic impairment (Child-Pugh class B)	
Elderly patients (age ≥75 y)	

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor/neprilysin inhibitor; eGFR = estimated glomerular filtration rate; PARADIGM-HF = Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in HF.

Guideline-Directed Medical Therapy (GDMT) in HFrEF

The treatment of heart failure with reduced ejection fraction (HFrEF) is guided by established protocols from the ACC/AHA/HFSA and ESC. These guidelines outline key algorithms for optimal management, focusing on the use of specific drug classes (such as ACE inhibitors, beta-blockers, and SGLT2 inhibitors) and interventions to improve survival and quality of life for HFrEF patients [23].

Figure 3: Guideline-Directed Medical Therapy (GDMT) in HFrEF



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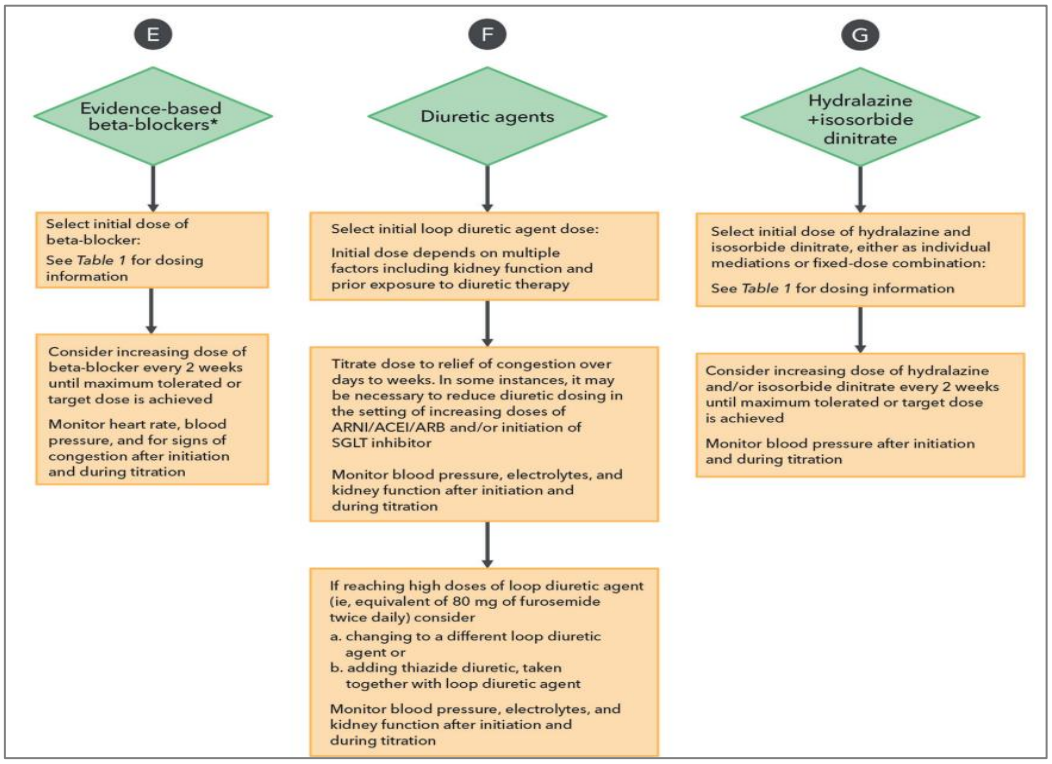

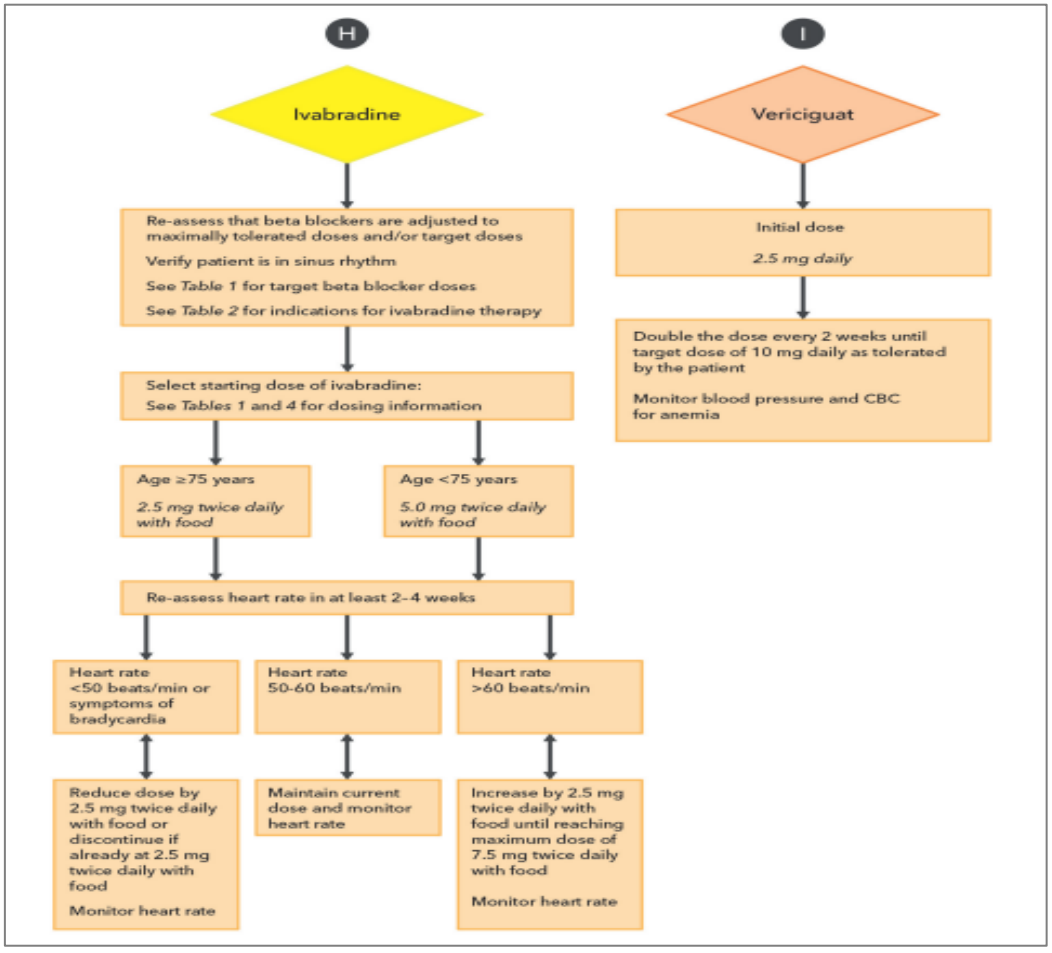

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor/neprilysin inhibitors; CBC = complete blood count; eGFR = estimated glomerular filtration rate; SGLT = sodium-glucose cotransporter.

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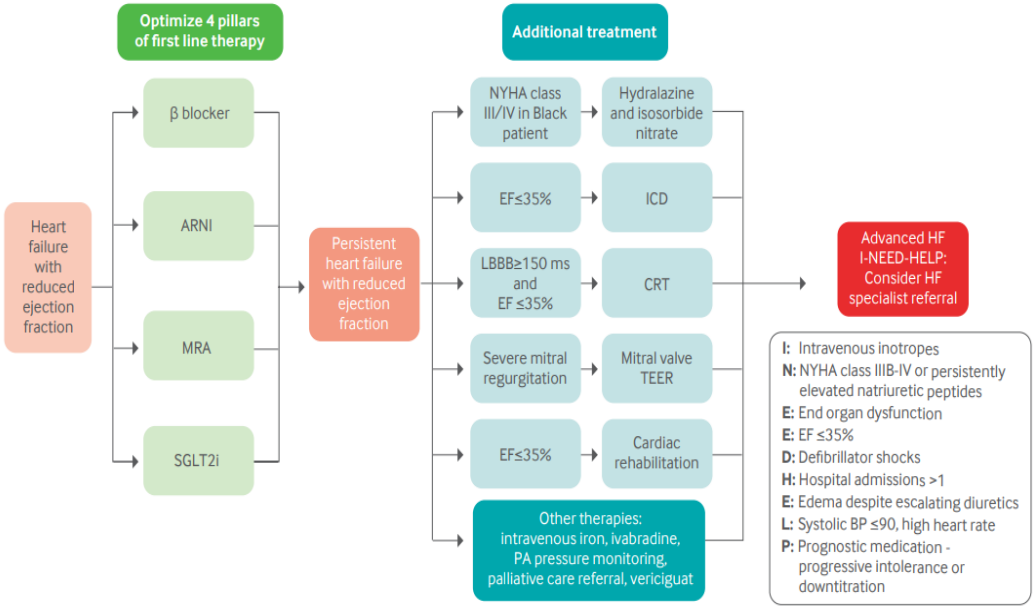
Prognosis and Risk Stratification in HFrEF

- NYHA Class: A key predictor, with higher NYHA classes associated with worse prognosis [24].
- Biomarkers: BNP and NT-proBNP are crucial biomarkers for diagnosing, assessing severity, and predicting prognosis in HFrEF. Elevated levels of these biomarkers, especially when rising, indicate high risk. Regular measurement helps guide clinical decisions, such as diuretic dosing and imaging for LV remodeling.
- NT-proBNP vs BNP: In patients on sacubitril/valsartan, BNP levels may rise due to neprilysin inhibition, but NT-proBNP tends to decrease consistently, making it more reliable in these cases. Severe kidney dysfunction can interfere with natriuretic peptide interpretation [25].
- Nonresponders: Patients whose BNP or NT-proBNP do not decrease with GDMT tend to have worse outcomes and may need closer monitoring or referral to advanced heart failure specialists.

Figure 4: Treatment strategies for heart failure.



ARNI=angiotensin receptor/neprilysin inhibitor therapy; BP=blood pressure; CRT=cardiac resynchronization therapy; EF=ejection fraction; HF=heart failure; ICD=implantable cardiac defibrillator; LBBB=left bundle branch block; MRA=mineralocorticoid receptor antagonist; NYHA=New York Heart Association; PA=pulmonary artery; SGLT2i=sodium glucose linked cotransporter 2 inhibitor; TEER=transcatheter edge- to edge repair.

In cases where heart failure progresses to an advanced stage, particularly in elderly patients or those ineligible for transplantation, palliative care becomes essential. Palliative care focuses on symptom management, psychosocial support, and advanced care planning, improving the quality of life for both patients and families. Early integration of palliative care into the treatment plan, alongside other forms of management, ensures a holistic, patient-centered approach, addressing not only physical but also emotional and psychological needs [25].

Effective communication between all members of the multidisciplinary team (MDT) is crucial to recognize when a patient's condition is deteriorating and when to initiate palliative measures, including mechanical circulatory support or end-of-life planning, based on the patient's preferences.

CONCLUSION

The future of HFrEF management is promising, driven by advancements in medications, device therapies, and multidisciplinary care. As we address current challenges and gaps in treatment, the continued commitment to research and innovation will play a crucial role in improving outcomes for patients with HFrEF. By fostering collaboration among healthcare professionals and incorporating new technologies, we can significantly enhance care and improve the quality of life for this growing patient population.

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