Heart Failure with Reduced Ejection Fraction

6

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6.1 Introduction

Heart failure (HF) is a syndrome that results in the inability of the heart to meet the metabolic demands of the body. Heart failure with reduced ejection fraction (HFrEF), previously called congestive heart failure due to its prominent clinical feature of fluid volume overload, or congestion, is defined as "a clinical diagnosis of heart failure with an ejection fraction <40%" and is often associated with left ventricular enlargement [1]. A proposed universal definition of HFrEF qualifies the diagnosis as a clinical syndrome that includes symptomatic HF with left ventricular ejection fraction (LVEF) ≤ 40% and presence of either elevated natriuretic peptides (i.e., brain natriuretic peptide [BNP]) or objective evidence of pulmonary or systemic congestion, i.e., via right heart catheterization [2]. Heart failure with preserved ejection fraction (HFpEF) represents approximately half of patients diagnosed with HF. HFpEF is currently defined as an LVEF ≥50% [1]. Treatment for HFpEF is available and addressed in a subsequent chapter. Heart failure with mildly reduced or midrange ejection fraction (HFmrEF) is defined as LVEF 41–49% with evidence of spontaneous or provoked increase in left ventricular filling pressures [1]. Patients with HFmrEF may benefit from similar therapies used in the treatment of HFrEF. Patients with HFrEF may have improvement in LVEF following implementation of goal-directed medical therapies (GDMT); however, these patients often continue to have changes in cardiac structure and function [1].

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Guideline-directed medical therapy should be continued in this subset of patients with HFrEF despite improvements in ejection fraction.

In this chapter, the epidemiology, etiology, diagnostic testing, GDMT, and device options for management of HFrEF will be presented.

6.2 Epidemiology

A predominant cause of HFrEF is coronary artery disease (CAD) and myocardial infarction (MI) although numerous other causes can result in left ventricular dilation and enlargement. Heart failure incidence and prevalence increases with advancing age and, based on the most recent data, approximately six million people ≥ age 20 have HF. Prevalence is expected to increase 46% by the year 2030 [3]. Older adult women (≥ age 80) and black men and women demonstrate the highest prevalence of heart failure [3]. Of heart failure hospitalizations, 50% are related to HFrEF. Heart failure is a chronic and progressive syndrome and 15–20% of patients diagnosed with HFrEF will develop worsening heart failure within 18 months of diagnosis [4]. Additionally, hospitalization due to HF exacerbation increases mortality risk by approximately 10% for each hospitalization [5].

6.3 Etiology

Heart failure can occur because of diseases of the pericardium, myocardium, endocardium, heart valves, coronary arteries, and/or certain metabolic or infectious disorders [6]. Etiology is often categorized into two classifications of cardiomyopathy (CMP): ischemic cardiomyopathy (ICM) and nonischemic cardiomyopathy (NCIM) [1]. The term dilated cardiomyopathy (DCM) is frequently used synonymously with NICM; however, the term DCM does not encompass all causes of NICM. Older studies examining outcomes of patients with HFrEF due to ICM versus DCM were mixed and the relationship between the etiology of HFrEF and outcome was unclear [7]. Patients with ICM or NICM can develop HFrEF. A data analysis of the Prospective Comparison of Angiotensin-receptor-neprilysin inhibitor (ARNI) with Angiotensin converting-enzyme inhibitor (ACEI) to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial demonstrated no differences in cardiovascular death or HF hospitalization between ICM and NICM groups when controlled for New York Heart Association (NYHA) functional class, and demographic, risk, and comorbid factors [8].

Cardiomyopathy can be classified according to anatomic or functional features (Table 6.1). Coronary artery disease and myocardial infarction (MI) cause myocardial remodeling and myocyte hypertrophy and destruction, resulting in ICM [9]. Dilated cardiomyopathy occurs as a consequence of myriad disorders affecting the

heart where the end result of the disease process is damage to the myocardium manifested as ventricular dilation and reduced myocardial contractility in the absence of hypertension or valvular disease [1, 10]. Other types of NICM occur as the result of processes that cause myocyte damage, infiltration, or fibrosis of myocardial tissues causing myocardial stiffening and restriction, or a thickening and hypertrophy of the myocardium [11].

Table 6.1 Classification of cardiomyopathy [1, 9–13]

Classification by disease type/ phenotype	Etiology
Ischemic cardiomyopathy (ICM)	Coronary artery disease
	Myocardial infarction
Nonischemic(NICM)/dilated cardiomyopathy (DCM)	Idiopathic
	Familial/genetic
	Hypertension
	Toxins:
	• Alcohol
	• Cocaine
	• Chemotherapy, i.e., anthracyclines
	• Ephedra, methylphenidate
	• Anabolic steroids
	• Thoracic radiation
	Nutritional:
	• Anorexia nervosa
	• Thiamine deficiency
	• Obesity
	Dystrophinopathies:
	• Duchenne muscular dystrophy
	• Becker's muscular dystrophy
	Tachycardia-induced cardiomyopathy
	LV noncompaction (LVNC)
	Arrhythmogenic right ventricular cardiomyopathy (ARVC)
Hypertrophic cardiomyopathy (HCM)	Idiopathic
	Familial/genetic
Restrictive/infiltrative cardiomyopathy	Amyloidosis
	Sarcoidosis
	Connective tissue disease:
	• Lupus erythematosus
	• Scleroderma
	• Hemochromatosis
Valvular cardiomyopathy	Mitral, tricuspid, pulmonary, or aortic valve disease
	Rheumatic heart disease

(continued)

Table 6.1 (continued)

Classification by disease type/ phenotype	Etiology
Peripartum cardiomyopathy	Pregnancy or postpartum associated heart failure
Inflammation or infection	Viral myocarditis:
	• Coxsackie
	• Parvovirus
	• Adenovirus
	• Echovirus
	• Influenza
	• HIV
	• SARS-CoV-2 (COVID-19)
	Protozoal infection:
	• Chagas disease
	Spirochete infection
	• Syphilis
	Giant cell myocarditis
Metabolic/endocrine disorders	Diabetes mellitus
	Hyperthyroidism
	Hypothyroidism
Stress-induced cardiomyopathy (Takotsubo)	Physical or emotional stress (catecholamine surge)

LV left ventricle, *HIV* human immunodeficiency virus

6.4 Prevention

A multitude of risk factors and disease processes increase the possibility a person will develop heart failure. Preventive strategies focus on elimination or management of modifiable risk factors (Table 6.2) [1, 14]. While many risk factors may not be eliminated, maintaining a healthy lifestyle is the most significant approach to preventing HF [15, 16]. Primary care providers (PCPs) play an essential role in recognizing HF risk factors among their patient population, implementing interventions to address modifiable risk factors and monitoring for development of or progression to HF. A team-based approach that evaluates the social determinates of health impacting treatment decisions and considers the patient's goals and preferences should be incorporated when developing plans of care [1].

Individuals with American College of Cardiology/American Heart Association (ACC/AHA) Stage A HF (Table 6.3) are at high risk for development of HF but have no structural cardiac changes or HF symptoms. Prevention strategies to ameliorate HF risk focus on management of comorbid disease processes and lifestyle and behavioral factors. The most significant comorbid diagnoses that promote progression of HF are hypertension, diabetes mellitus, metabolic syndrome, and history of

Table 6.2 HFrEF risk factors [1, 10]

Modifiable
• Hypertension
• Diabetes mellitus
• Metabolic syndrome
• Atherosclerotic disease
• Dyslipidemia
• Smoking/tobacco use
• Physical inactivity
• Overweight/obesity
• Excessive alcohol consumption
• Cardiotoxic over the counter or medicinal substances in excessive doses or prolonged use, e.g., anabolic steroids, amphetamines, ephedra, decongestants, nonsteroidal anti-inflammatories
Nonmodifiable
• Cardiotoxic chemotherapy, e.g., anthracyclines, trastuzumab, cyclophosphamide
• Thoracic radiation
• Family history of sudden cardiac death
• Family history of premature CAD: age < 55 males, age < 65 females
• Conduction system disease, e.g., atrial fibrillation
• Muscular dystrophy

atherosclerotic cardiovascular disease (ASCVD), particularly MI or CAD [1, 14]. Hypertension control is the most effective strategy in preventing new onset HF [17].

Assessment of ASCVD risk is the basis for determining primary prevention strategies [15]. Asymptomatic adults aged 40–75 should be screened; screening adults > age 20 every 4–6 years should be considered. Eight primary preventive measures have been shown to avert ASCVD events leading to HF progression and include weight reduction if overweight or obese (BMI $\geq$ 25.9 kg/m^2), increased physical activity, blood pressure, cholesterol and glycemic control, smoking cessation, adherence to a healthy diet, and renal function monitoring, as well as implementation of guideline-based pharmacologic interventions for management of comorbidities [15, 16]. Family history of premature ASCVD (age < 55 males, age < 65 females); metabolic syndrome; chronic kidney disease; chronic inflammatory conditions, e.g., lupus, rheumatoid arthritis, HIV/AIDS; history of premature menopause (< age 40); history of preeclampsia; high-risk race or ethnicity (South Asian ancestry); hypertriglyceridemia; extracardiac vascular disorders, e.g., erectile dysfunction, claudication, or peripheral arterial vascular disease (PAD) are factors that revise a patient's 10-year ASCVD risk estimation and should be included in patient assessment. Individuals with HF Stages B–D (Table 6.3) should also undergo aggressive management of cardiovascular risk factors as secondary prevention strategies to avoid HF progression [16].

Table 6.3 Heart failure stages and functional classification [1]

ACC/AHA stages of HF			NYHA functional classification
A	*At-risk for heart failure* At high risk for HF without current or previous signs/symptoms of HF and without structural heart disease or abnormal biomarkers	None	
B	*Pre-heart failure* Structural heart disease without current or previous signs/symptoms of HF without abnormal biomarkers	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF
C	*Symptomatic heart failure* Structural heart disease with prior or current signs/symptoms of HF with structural heart disease, or evidence of increased filling pressures, or risk factors and increased BNP or cardiac troponin in absence of competing diagnosis	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF
		II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF
		III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF
		IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest
D	*Advanced heart failure* Refractory HF despite attempts to optimize GDMT	IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest

ACC American College of Cardiology, *AHA* American Heart Association, *NYHA* New York Heart Association

6.5 Outpatient Management

6.5.1 Diagnosis and Evaluation

The typical primary care provider managing 2000 patients is likely to have 40–50 patients with HF and roughly five newly diagnosed cases per year [18]. Although relatively common, the individual practitioner will likely not become an expert in HFrEF diagnosis. Clinical diagnosis can present a major challenge as patients may exhibit a variety of signs and symptoms, many of which are not specific to HF. Patients with HF often have several comorbid conditions, further complicating the clinical presentation [19]. Additionally, individuals not typically thought to be predisposed to HF, e.g., young adults, pregnant or postpartum women, may be misdiagnosed.

6.5.2 Patient History

A detailed history is important to identify any cardiac and noncardiac disorders that may contribute to the development or progression of HF [1]. Elements of the patient history should include chief complaint, history of present illness (HPI), past medical history, family history, social history and habits, review of systems, and a functional assessment (Table 6.4). Risk assessment can be useful to estimate subsequent

Table 6.4 Heart failure patient history [20]

HPI	Chief complaint Signs/symptoms Hospitalizations Emergency department visits Medications & supplements Allergies/intolerances	
Past medical history	*Cardiac conditions* Coronary artery disease Myocardial infarction Cardiac surgery/procedures Hypertension *Infiltrative disease* Amyloidosis Sarcoidosis *Hereditary disease* Cardiomyopathy Hemochromatosis Sickle cell trait Thalassemia *Dysrhythmias* Devices Pacemaker Cardiac resynchronization therapy (CRT) Implanted cardioverter defibrillator (ICD)	*Noncardiac conditions* Diabetes mellitus Hyper/hypothyroidism Peripheral vascular disease *Connective tissue disorders* Lupus erythematosus Scleroderma *Infectious disease* Hepatitis C Human immunodeficiency virus (HIV) Chronic obstructive pulmonary disease (COPD) Renal insufficiency/chronic kidney disease Mediastinal irradiation Pheochromocytoma Anemia Obesity
Family history	Coronary artery disease Cerebrovascular accident or transient ischemic attack Cardiomyopathy (3 generations for idiopathic/familial) Sudden cardiac death Hypertension Hyperlipidemia	
Social history/social determinates of health	Social support system Family Marital status Care partner Childcare Financial resources/strain Insurance/access to care Education Work/profession	Tobacco/alcohol Illicit drugs Religion/culture Transportation Food insecurity Health literacy Mental health Exposure to adversity Violence Trauma Personal safety Housing/utilities

mortality risk, including utilization of biomarkers and a variety of risk models that guide treatment plans [1, 21, 22]. Available risk score models frequently used in the chronic HF population include the Seattle Heart Failure Model, Heart Failure Survival Score, and the CHARM and CORONA Risk Scores [1]. Functional assessment and ability to complete activities of daily living are helpful in assessing the overall degree of limitation. The 6-min walk can be easily evaluated in all settings and is a measure of exercise capacity that can be trended over time following the initial diagnosis of HF [23] Functional assessement often correlates with NYHA heart failure classification and should be monitored over time to evaluate changes in severity of illness, including signs and symptoms of decompensation [1].

6.5.3 Physical Exam

A primary goal in assessment of the patient with HF is to determine the extent and severity of disease. Physical examination focuses primarily on the cardiovascular and pulmonary systems. Volume status, vital signs, and weight should be evaluated at every patient encounter [1]. Orthostatic hypotension can be common and may be related to vasodilation, low cardiac output, and/or volume depletion.

The HF-focused exam includes [24]:

- General inspection—skin/nailbed color, mental status, respiratory effort.
- Jugular venous pressure (JVP)—normal <8 cm when assessed at 45-degree angle.
- Heart sounds/murmurs.
- Lung sounds.
- Hepatojugular reflux (HJR)/abdominojugular test—increase in JVP when manual pressure applied over the liver.
- Peripheral edema/skin temperature.

A variety of abnormal assessment findings may be seen in the HF population. Findings may include tachycardia and tachypnea, elevated JVP, rales or crackles, decreased breath sounds, S3 heart sound, displaced point of maximal impulse (PMI), ascites, HJR, reduced strength of peripheral pulses, cyanosis, and cardiac cachexia [20]. Tachycardia is typically a compensatory response to low cardiac output. Cardiac enlargement is detected by palpation, with the PMI laterally displaced or presence of a precordial heave. A third heart sound, S3, is associated with congestion and may be one of the earliest signs of cardiac decompensation due to HF [24]. Murmurs are indicative of valvular dysfunction. Mitral regurgitation can occur with increased LV mass and dilation of the valve annulus. Both elevation of JVP and positive HJR reflect venous congestion [20, 24]. Respiratory rate and pattern reflect the degree of pulmonary compromise. Crackles from transudative fluid in the alveolar spaces may be auscultated, but clear breath sounds do not exclude the presence of pulmonary edema [1]. Peripheral edema is most common in the lower extremities, ankles, and feet. In severe, untreated fluid volume overload, anasarca may occur. Cool and mottled extremities are associated with low cardiac output. Cardiac cachexia and muscle wasting are not well understood but are a poor prognostic sign

[25]. See also Chap. 4 for more details of the physical exam for presence and severity of HF.

6.5.4 Diagnostic Evaluation

If a diagnosis of HFrEF is suspected, initial evaluation includes measurement of natriuretic peptides, electrocardiography, and chest X-ray. Signs of congestion and cardiomegaly on chest X-ray are sensitive for HF [25]. Transthoracic echocardiogram remains the gold standard for evaluation of ejection fraction (EF), left and right ventricular mass, chamber size, valvular dysfunction, and pericardial effusion [1]. Routine, repeat measurement of left ventricular (LV) function is not warranted in the absence of a change in clinical status [1]. New patient HF evaluation should also incorporate laboratory analysis to establish baseline levels and evaluate for disorders that contribute to or exacerbate HF and includes electrolytes, hepatic and renal function, thyroid function, diabetes mellitus, and anemia. Genetic testing is warranted for familial or genetically transmitted disorders affecting the myocardium. Based on the 2017 HF guidelines, measurement of natriuretic peptides should be utilized to assist in the diagnosis or exclusion of HF, to aid in the determination of prognosis, and for risk stratification [26].

The etiology of HFrEF is often ischemia; newly diagnosed patients typically require an evaluation for CAD. Left heart cardiac catheterization (LHC) with coronary angiography is the benchmark diagnostic tool for identification of obstructive epicardial CAD. Noninvasive evaluation may be considered for patients who are deemed low risk for atherosclerosis. Cardiac magnetic resonance imaging (cMRI), positron emission tomography (PET), or technetium pyrophosphate scintigraphy (PYP) may be indicated, depending upon clinical presentation and suspicion of specific underlying illness, such as myocarditis or amyloidosis [25]. Right heart catheterization (RHC) to evaluate hemodynamic status and cardiopulmonary exercise stress testing (CPXT) to evaluate functional capacity are utilized to assess degree of cardiac decompensation, response to GDMT, and when evaluating an individual's candidacy for advanced therapies, such as ventricular assist devices (VAD) and cardiac transplantation. Endomyocardial biopsy is not routinely performed but can be helpful in diagnosing myocarditis, post-transplant rejection, or other infiltrative processes (Table 6.5) [1].

6.5.5 Clinical Presentation

Patients with HF may present initially with a wide variety of symptoms that are vague and nonspecific, confounding the diagnosis. Dyspnea, at rest or with exertion, and fatigue are often the predominate symptoms prompting an individual to seek treatment. Additional cardinal symptoms include fluid retention, orthopnea, and paroxysmal nocturnal dyspnea. Patients may complain of abdominal pain and early satiety due to splanchnic and liver congestion [1, 28]. Bendopnea, shortness of breath when

Table 6.5 Diagnostic tools for evaluation of HFrEF [1, 25–27]

Laboratory studies	Diagnostic imaging
Natriuretic peptides	12 Lead EKG
Biomarkers (e.g., troponin, ST2)	Chest X-ray
Complete blood count	2D echocardiogram
Basic metabolic profile	Cardiac catheterization
Hepatic function panel	Stress testing
Iron studies	MRI
Urinalysis	PET
Thyroid function tests	PYP scan
Hemoglobin A1c	CPXT
Lipid panel	Endomyocardial biopsy
Genetic testing	

Table 6.6 Signs and symptoms of left and right ventricular failure [1, 28, 30]

LV failure	RV failure
Shortness of breath	Jugular venous distention
Tachypnea	Edema
Orthopnea	Abdominal distension
Benopnea	Hepatomegaly
Cough	Ascites
Crackles/rales	Anorexia/early satiety
Pleural effusion	Nausea
	Right upper quadrant pain
	Anasarca

bending forward, is associated with advanced NYHA classification and greater mortality [29]. Signs and symptoms may be defined based upon the primary targets of congestion. Left-sided symptoms are primarily reflected in the lungs and pulmonary system whereas right-sided symptoms appear in the peripheral vasculature (Table 6.6).

6.5.6 Guideline-Directed Medical Therapy

Utilization of GDMT is centered upon specific treatment recommendations as categorized by the ACC/AHA heart failure staging system and NYHA classification (Table 6.3) [1]. GDMT for HFrEF focuses on patients with Stage C and D HF. NYHA class will vary based upon changes in clinical condition and symptoms. Overall management goals include symptom control, prevention of disease progression, and reduction of HF hospitalization rates and mortality.

The landscape of evidence-based medications for HFrEF continues to evolve but the cornerstone remains neurohormonal blockade to counteract the deleterious effects of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS). Angiotensin converting enzyme inhibitors, ARBs, ARNI, and aldosterone antagonists/mineralocorticoid receptor agonists (AA/MRA) all have morality benefit in patients with HF [1, 26]. Based on the totality of data

surrounding ARNI, sacubitril/valsartan (the first and only commercially available ARNI in the USA) is the preferred RAAS antagonist in HFrEF [31]. Although ACEI and ARB medications are used interchangeably and are considered to have a "class effect," only three beta blockers are approved for use in HF—bisoprolol, carvedilol, and metoprolol succinate [1]. Diuretics are commonly prescribed to manage congestion and volume overload and are solely for symptom control. Hydralazine in combination with nitrates is an alternative for those patients who have contraindications or intolerance to ACEI/ARB/ARNI and in special populations, such as African Americans. Digoxin may be prescribed to improve symptoms and reduce HF hospitalization rates. Ivabradine acts at the level of the sinoatrial node to lower heart rate without compromising blood pressure and was demonstrated to improve HF hospitalization rates in the Systolic Heart Failure Treatment with the I_f Inhibitor Trial (SHIFT) [32].

Additional therapies continue to gain Food and Drug Administration (FDA) approval as new pathological targets have been identified to improve symptoms and/or outcomes for patients with HFrEF, such as the guanylyl cyclase (sCG) stimulators and the sodium-glucose co-transporter-2 (SGLT2) inhibitors [31]. Vericiguat, a sCG stimulator, received FDA approval in January 2021 and is the first treatment for chronic heart failure approved specifically for patients following a hospitalization for HF or in need of outpatient intravenous (IV) diuretics. Based on the results of the pivotal, phase III Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction (VICTORIA) trial, vericiguat is indicated to reduce the risk of cardiovascular death and HF hospitalization among patients with symptomatic chronic HF [33]. Vericiguat is adjunctive therapy to baseline GDMT and works through the nitric oxide pathway to increase smooth muscle relaxation and vasodilation [34].

Although the complete mechanism of action remains unclear, SGLT2 inhibition has repeatedly shown benefit among the HFrEF population in patients with and without diabetes mellitus [31]. SGLT2 inhibition promotes diuresis and natriuresis (sodium loss), leading to reduction in preload, blood pressure, arterial stiffness, and afterload, thereby improving subendocardial blood flow. SGLT2 inhibition is also associated with a shift to ketone-based myocardial metabolism and preservation of renal function [35]. Two SGLT2 agents, empagliflozin and dapagliflozin, have an approved indication for HF. SGLT2 inhibition received a Class IA recommendation with publication of the 2022 HF guideline to reduce HF hospitalization and reduce cardiovascular mortality [1]. Table 6.7 outlines the aforementioned indications and neurohormonal targets along with the appropriate agents that are recommended for HFrEF medical therapy [36].

6.5.7 Initiation, Titration, and Optimization

HF medical regimens are increasing in complexity and patients often have multiple comorbid conditions, complicating management for both patients and clinicians. The current treatment algorithm for GDMT in HFrEF Stage C and D is depicted in Fig. 6.1.

Table 6.7 Indications for medical therapy in HFrEF. Adapted [36]

Indication/therapy target	Agent
RAAS inhibition	ACEI, ARB, ARNI AA/MRA (spironolactone, eplerenone)
SNS inhibition	Beta blockers (bisoprolol, carvedilol, metoprolol succinate)
SGLT2 inhibition	SGLT2 inhibitors (dapagliflozin and empagliflozin)
Guanylyl cyclase stimulator (sCG stimulator)	Soluble sCG stimulator (vericiguat)
HR/HF hospitalization reduction: Beta adrenergic receptors Sodium/potassium ATPase pump HCN-gated channel	Beta blockers Cardiac glycosides (digoxin) HCN-gated channel inhibitor (ivabradine)
Congestion: Sodium inhibition in the nephron	Diuretics (loop, thiazide)
Vasodilation: Arterioles (afterload) Intracellular cyclic-GMP (preload)	Hydralazine + nitrates (African Americans, or ACE/ARB/ARNI intolerant)

RAAS renin-angiotensin-aldosterone system, *SNS* sympathetic nervous system, *ACEI* angiotensin converting enzyme inhibitor, *ARB* angiotensin 2 receptor blocker, *ARNI* angiotensin receptor neprilysin inhibitor, *MRA* mineralocorticoid receptor agonist, *SGLT-2* sodium-glucose cotransport-2, *HR* heart rate, *HF* heart failure, *HCN* hyperpolarization-activated cyclic nucleotide, *DCT* distal convoluted tubule, *GMP* guanosine monophosphate

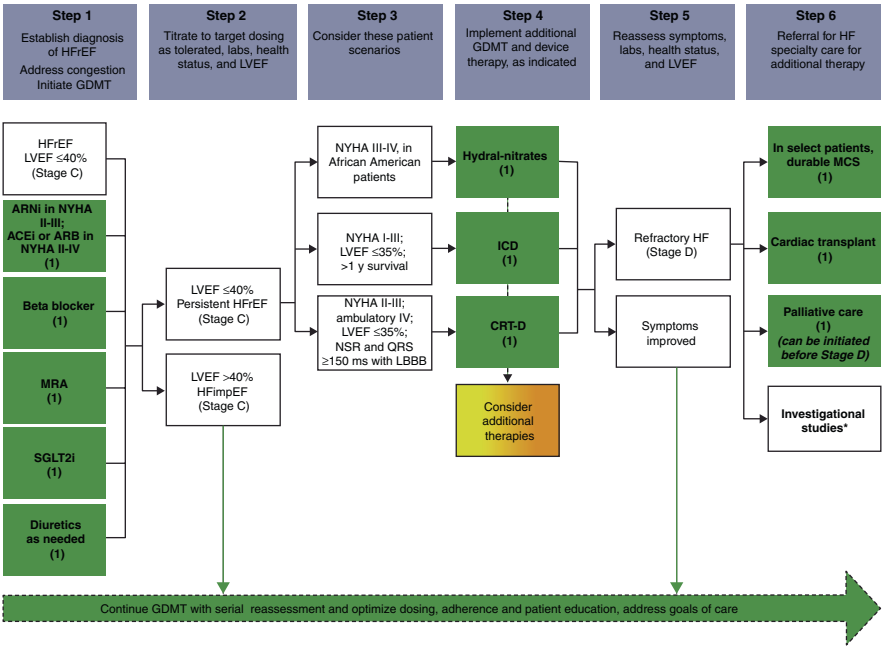

Fig. 6.1 Treatment algorithm for GDMT [1]. [Reprinted from Journal of Cardiac Failure, 79 (17), Heidenreich P, Bozkurt B, Aguilar D, et al. AHA/ACC/HFSA Guideline for the Management of Heart Failure, e263–e421, copyright (2022), with permission from Elsevier]

GDMT is shown to reduce morbidity and mortality within 30 days of initiation [37]. Optimizing GDMT and promoting patient adherence remains a challenging task for clinicians. Despite clear guidelines for the management of HFrEF, results from the Change the Management of Patients with Heart Failure (CHAMP-HF) registry showed major gaps in utilization of evidence-based medical therapy, highlighting a significant opportunity to improve clinical care and outcomes for the HFrEF population [38]. Practical strategies to promote adherence and optimize GDMT include [1, 6, 31, 39]:

- Prioritize therapies with the greatest therapeutic benefit: ARNI, beta blockers, AA/MRA, and SGLT2 inhibitors.
- Initiate medications at low doses and up-titrate as tolerated.
- Minimize diuretics to the lowest possible dose to maintain euvolemia.
- Avoid medication up-titration if volume depleted or HF decompensated.
- Schedule medication dosing to avoid excessive fluctuations in blood pressure or hypotension.
- Monitor renal function, electrolytes, and cardiac-specific biomarkers (BNP, NTproBNP, Troponin) to assess for HF exacerbation and aide clinical decision making.
- Assess affordability and access to prescribed medication regimen.
- Reconcile medications at every visit. Discuss side effects and reinforce benefits.
- Simplify regimen when possible; deprescribe all nonessential medications and supplements.
- Employ "teach back" method to assess recall and understanding. Include caregivers in patient education.

6.5.8 Adjunctive Therapies

Patients with HFrEF may benefit from adjunctive therapies to augment GDMT and improve quality of life. Revascularization procedures are recommended for patients with coronary ischemia, suitable coronary anatomy, and viable myocardium. Hyperkalemia is a clinical adverse effect of RAAS inhibition, often limiting initiation or up-titration of ACE inhibitors, ARBs, AA/MRAs, or ARNI. Potassium binders may be considered to allow continuation of GDTM. Omega-3 polyunsaturated fatty acid supplementation is a reasonable consideration to reduce mortality and cardiovascular hospitalizations. Mitral valve surgery or transcatheter mitral valve repair is indicated for patients with secondary, or functional, mitral regurgitation [1].

Many adjunctive therapies have not improved outcomes in the HFrEF population. Anticoagulation is not recommended without the presence of comorbid conditions, such as atrial fibrillation or prior thrombotic/embolic event. Statins are not beneficial when solely prescribed for the diagnosis of heart failure. Nutritional supplementation and hormonal therapies, other than to correct confirmed deficiencies, are not recommended. Continuous inotropic infusions are not indicated except for palliation or as a "bridge" to advanced therapies [1]. Medications known to adversely influence the clinical status of patients with HFrEF should be avoided,

including calcium channel blockers, most antiarrhythmic medications, nonsteroidal anti-inflammatory agents, and thiazolidinediones [1].

6.5.9 Nonpharmacological Interventions

In addition to standard medical therapy, nonpharmacological interventions managed collaboratively by the primary care and cardiology clinicians can augment HF patient stability, quality of life, adherence, and patient engagement in self-care (Table 6.8).

6.5.10 Device Therapy

The therapeutic benefits of device therapy for the treatment of HFrEF are well established and a subset of patients will be candidates for implantable devices once GDMT is optimized [41–43]. Implantable device therapy should only be considered in patients receiving optimal GDMT.

Implantable cardioverter defibrillators (ICDs) protect HF patients from sudden cardiac death (SCD) due to cardiac dysrhythmias; however, frequent shocks may decrease quality of life and result in significant stress and anxiety [1]. Use of antiarrhythmic medications, catheter ablation of arrhythmogenic myocardium, and refined ICD and cardiac resynchronization therapy (CRT) programming can decrease the frequency of dysrhythmias requiring shocks to restore normal sinus rhythm [6].

Wearable cardiac defibrillators (WCD) are available for patients at risk for sudden cardiac death who do not qualify for ICD implantation. WCDs provide an option for protection when the risk of SCD is unclear, such as after acute MI and coronary revascularization procedures in the setting of low EF, prior to initiation of GDMT, those awaiting mechanical circulatory support implantation and/or cardiac transplantation, and patients with an active contraindication to device implantation, such as infection [44].

In approximately one third of patients, HF progression is associated with a prolongation of the QRS interval and asynchronous contraction between the right and

Table 6.8 Nonpharmacologic interventions for heart failure [1, 40]

Individualized patient education
Weight management
Physical activity/cardiac rehabilitation
Smoking cessation
Alcohol moderation/restriction
Avoid excessive sodium intake
Fluid restriction (as indicated)
Continuous positive airway pressure (CPAP) for sleep apnea
Primary disease prevention screenings (mammogram, colonoscopy, etc.)
Influenza/pneumococcal/COVID-19 vaccination

left ventricle, resulting in decreased efficiency of cardiac performance. Cardiac resynchronization therapy can improve ventricular function, decrease mitral regurgitation, reverse ventricular remodeling, and improve EF [1]. More recently, device therapy options have expanded to select patients with low to moderate EF and a narrow QRS complex (Table 6.9). Although the exact mechanism of action differs slightly between devices, all are designed to modulate the SNS [45–47].

HF hospitalization and readmission rates remain a target for improved clinical outcomes. Despite the Hospital Readmission Reduction Program (HRRP), 30- and 90-day readmission rates increased from 2010 to 2017 [48]. Ambulatory pulmonary artery pressure monitoring can largely reduce hospitalization for patients with NYHA class II and III heart failure [49, 50]. Wireless implantable hemodynamic monitoring allows for improved heart failure management by early detection of changes in pulmonary pressures. The CardioMEMS™ HF System (Fig. 6.2) is the first and only FDA-approved wireless heart failure monitoring system proven to reduce hospitalization for both HFrEF and heart failure with preserved ejection fraction (HFpEF) [50, 51].

Table 6.9 Novel devices for HFrEF with narrow QRS complex [45–47]

Device	Barostim™	Optimizer® Smart	Cardionomic™ Pulmonary Neuromodulation System (CPNS)
Manufacturer	CVRx	Impulse Dynamics	Cardionomic
Mechanism of action	Activates baroreceptors in carotid artery, increases parasympathetic tone, decreases sympathetic drive	SNS modulation to increase contractile force, no increase in oxygen consumption	SNS stimulation to increase contractility and MAP, no change in heart rate
Indication	• EF < 35	• EF 25–45	• EF < 50
	• NYHA II or III	• Narrow QRS	• SBP > 80
	• NO indication for CRT	• NO indication for CRT	• NO CRT/ICD
	• NT pro BNP < 1600		• NSR
Insertion	Carotid stimulator and pulse generator; requires vascular surgeon and electrophysiology	Pulse generator and 2 leads—placed by electrophysiology	IJ insertion, 16 Fr—placed by interventional cardiology or electrophysiology
Clinical benefits	• Increased QoL	• Increased QoL	• "Device inotropy"
	• Increased 6 MWT	• Increased 6 MWT	• Increase SV, contractility, MAP
	• Improvement in NYHA Class	• Improvement in NYHA Class	
	• Decreased BNP	• Increased peak VO_2	
Cost	$35K	$23K	TBD
FDA approval	August, 2019	March, 2019	FDA approved pilot study initiated April, 2021

Mitral regurgitation (MR) is common in the HFrEF population as LV dilatation leads to poor coaptation of the mitral valve, known commonly as functional or secondary MR. Severity of functional MR is strongly associated with decreased quality of life and increased heart failure hospitalization and mortality [52]. Management of valvular heart disease has dramatically changed with the advent of transcatheter valve procedures. MitraClip™ is a minimally invasive, catheter-based device which grasps and coapts the mitral valve leaflets, thus reducing MR throughout the cardiac cycle [53]. MitraClip™, depicted in Fig. 6.3, provides a

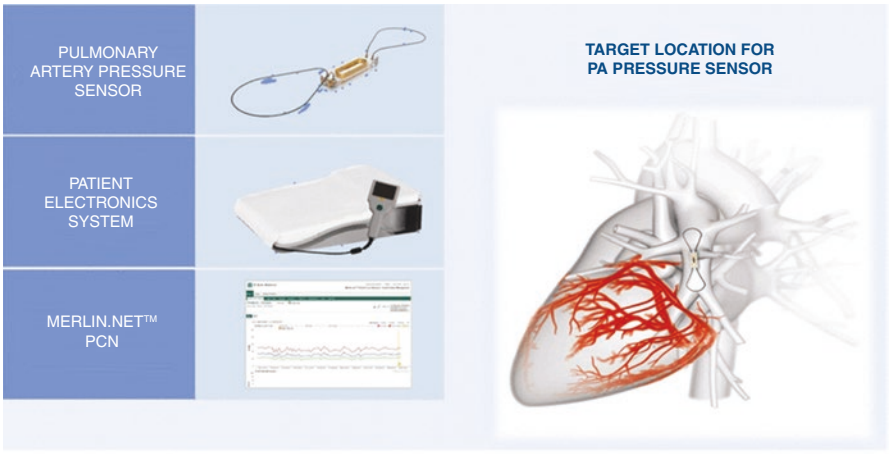

Fig. 6.2 CardioMems™ HF System. [Abbott, Abbott "A," CardioMEMS, HeartMate, HeartMate 3, and MitraClip are trademarks of Abbott or its related companies. Reproduced with permission of Abbott, © 2021. All rights reserved]

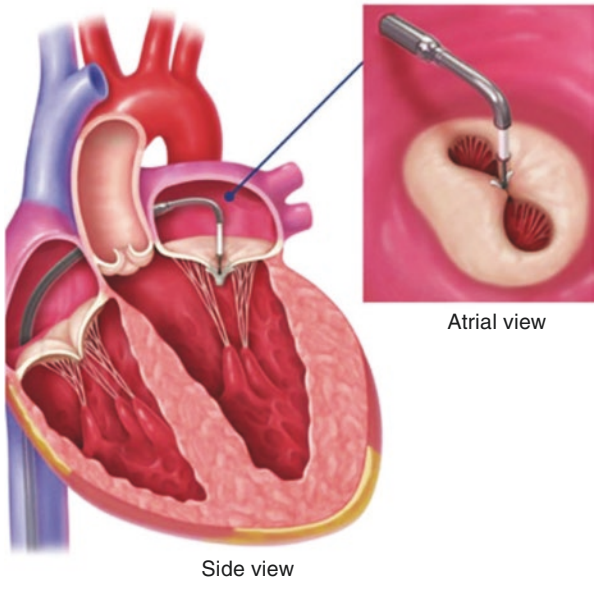

Fig. 6.3 MitraClip™ transcatheter mitral valve repair (TMVr) [54]. [Abbott, Abbott "A," CardioMEMS, HeartMate, HeartMate 3, and MitraClip are trademarks of Abbott or its related companies. Reproduced with permission of Abbott, © 2021. All rights reserved]

safe and effective option for patients, reducing all-cause mortality and HF hospitalization while improving quality of life [54].

6.6 Putting It All Together

6.6.1 Case Study

6.6.1.1 Subjective HPI

A. Johnson is a 62-year-old, African American male recently discharged from the hospital with a new diagnosis of nonischemic cardiomyopathy, ACC/AHA Stage C, NYHA class III. He had a left heart cardiac catheterization (LHC) while hospitalized and was found to have nonobstructive CAD. His LVEF is 25–30% per transthoracic echocardiogram (TTE) and found to have moderate mitral regurgitation. He denies syncope and/or presyncope. No chest pain, palpitations, orthopnea, dyspnea, PND, lower extremity edema, or abdominal bloating.

6.6.1.2 Past Medical History

Hypertension, uncontrolled.
Obesity—BMI 31 kg/m^2.
Obstructive sleep apnea (untreated).
No history of tobacco or substance abuse.
Reports adherence with medications and dietary restrictions.

6.6.1.3 Current Medical Regimen

Aspirin 81 mg daily.
Atorvastatin 20 mg once a day.
Carvedilol 3.125 mg twice daily.
Sacubitril/valsartan 26/24 mg twice daily.
Spironolactone 12.5 mg daily.
Furosemide 80 mg once daily.

6.6.1.4 Review of Systems

No acute distress.
Daily weights stable.
Denies nausea & early satiety.
Dyspnea with moderate exertion but has improved.
Occasional palpitations with activity

6.6.2 Objective

Objective: Vital signs: BP 138/78 HR 82; RR 20, oxygen saturation 98% on room air; Temp 98.7 °F. Weight 212 pounds. Physical exam: Lungs clear, JVP 4–6 cm

at 90°F, no HJR. Heart regular rate and rhythm, IV/VI apical systolic murmur, PMI laterally displaced. No LE edema, bilaterally extremities are warm.

Labs results (day of visit): Sodium 145 mmol/L; Potassium 4.0 mmol/L; BUN 17 mg/dL; Creatinine 1.24 mg/dL (eGFR 77.0 > =6.0 mL/min/1.73 m^2), NTproBNP 200 pg/mL.

TTE (2 weeks ago) LVEF 25–30%, LVIDD 6.0 cm, mild-moderate mitral regurgitation no other valvular abnormalities.

EKG: Sinus rhythm, left bundle branch block.

6.6.3 Assessment

Mr. Johnson presents to office post hospital discharge. Symptomatically and hemodynamically stable. He is warm and euvolemic with adequate blood pressure and heart rate for uptitration of GDMT.

6.6.4 Plan

1. Increase carvedilol 6.25 mg twice daily for improved heart rate control and improved afterload reduction.
2. Add Dapagliflozin 10 mg daily.
3. No other medications changes on this visit.
4. Lifestyle modification—weight loss.
5. Referral for sleep apnea evaluation and CPAP consideration.
6. Return to clinic in 1 month with repeat labs BMP, NTproBNP.
7. Repeat echocardiogram in 3 months—Electrophysiology referral if EF not improved.

6.6.5 Heart Failure with Reduced Ejection Fraction: Clinical Considerations

- Initiate comprehensive, disease modifying GDMT at time of diagnosis.
- Start with low doses, prioritize beta blocker up-titration.
- Benefits of ARNI/BB/MRA/SGLT2i are demonstrated within 30 days of initiation.
- Cumulative benefits of GDMT within 30 days are incremental and additive, with an overall relative risk reduction >75%.
- Median survival with GDMT at maximally tolerated doses is extended approximately 6 years.
- [1, 55].

6.7 Conclusion

Heart failure with reduced ejection fraction continues to increase in incidence with significant morbidity and mortality accompanied by diminished quality of life despite advances in targeted, evidence-based medical and device therapies. HF remains a substantial burden to patients, caregivers, clinicians, and the health care system. As clinical presentation is often insidious and nonspecific, accurate evaluation and diagnosis can be challenging for primary care teams. Implementation of primary prevention strategies to aggressively manage risk factors may prevent new-onset HF. Adherence and rapid adoption of GDMT and device therapies can significantly improve clinical outcomes and decrease the overall economic burden of HF associated with repeat hospitalizations. Primary care teams can play a vital role in the complex management of heart failure and should refer to cardiology and/or specialized heart failure programs when patients fail GDMT and/or have recurrent HF hospitalizations.

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