Chapter 1
Heart Failure, Introduction

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Abstract Heart failure (HF) is a growing worldwide epidemic that results in significant morbidity and mortality in the aging population. HF is an important contributor to both the burden and cost of national healthcare expenditures, with more older Americans hospitalized for HF than for any other medical condition. Over the last two decades, there has been considerable progress in the treatment of HF with angiotensin-converting-enzyme (ACE) inhibitors, aldosterone antagonists, beta-receptor blockers, and resynchronization therapy. Nevertheless, HF is still associated with a poor prognosis. Approximately half of the people who develop HF die within 5 years of diagnosis. The search for better treatments for HF is one of the major challenges in cardiology. Greater understanding of the molecular dynamics and humoral perturbation will lead to newer HF treatment. In this chapter, different etiologies of HF, a systematic approach to the evaluation of a patient with HF, current strategies for the treatment, and emerging therapies in this field are discussed.

Keywords Heart failure • Emerging therapies • Guideline-directed medical treatment • Stages of heart failure • Devices in HF

1.1 Introduction

Heart failure (HF) is an important healthcare issue because of its high prevalence, mortality, morbidity, and cost of care. It is estimated that more than eight million Americans will have HF by 2030 [1]. HF incidence increases with age, rising from

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approximately 20 per 1,000 individuals 65–69 years of age to >80 per 1,000 individuals among those >85 years of age [2]. Because of aging of the population, the increase in HF will be greatest for older Americans. Approximately half of people who develop HF die within 5 years of diagnosis [3]. One in nine deaths includes HF as contributing cause [3]. Total costs, including indirect costs for HF, are expected to increase from $31 billion in 2012 to $70 billion in 2030 [1].

Ischemic heart disease, hypertension, and valvular heart disease are the most common causes of HF. Less common causes include diabetes; genetic cardiomyopathies and muscular dystrophies; autoimmune and collagen vascular diseases; toxic cardiomyopathies, including alcohol or illicit drugs such cocaine; chemotherapy-induced cardiomyopathies (e.g., Adriamycin); myocarditis and viral cardiomyopathy; postpartum cardiomyopathy; tachycardia-mediated HF; infiltrative disorders, such as sarcoidosis, hemochromatosis, and amyloidosis; high-output states; and stress-induced (takotsubo) cardiomyopathy.

1.2 Classifications of HF

Commonly used classifications of HF include classifications according to the stages of HF disease progression; symptoms and functional capacity of patients; etiology of HF; and left ventricular (LV) function and structure.

1.2.1 HF Defined According to Left Ventricular Systolic Function

HF with reduced left ventricular ejection fraction (HFrEF) The definition of HFrEF has varied but usually implies EF less than 40–50 %. In the 2013 ACCF/AHA guideline for the management of HF, HFrEF is defined as the clinical diagnosis of HF and LVEF ≤40 %. Patients with EF >40 and less than 50 % are recognized as borderline or intermediate group, with their characteristics, treatment patterns, and outcomes appear similar to those of patients with HF with preserved EF (HFpEF).

HF with preserved left ventricular ejection fraction (HFpEF) Approximately half of the HF patients enrolled in the clinical trials or hospitalized HF patients in acute HF registries have HFpEF. Currently there are no specific treatment strategies for HFpEF other than treatment of underlying risk factors and comorbidities, such as hypertension, diabetes, obesity, coronary artery disease, and atrial fibrillation, which are quite common in patients with HFpEF.

1.2.2 HF Defined According to Etiology and LV Structural and Hemodynamic Changes

In clinical practice, the etiology of HF has often been placed into two categories: ischemic and nonischemic cardiomyopathy. In general practice and clinical research trials, the term ischemic cardiomyopathy usually refers to cardiomyopathy due to ischemic heart disease. Though this approach may be practical, it fails to recognize that the term "nonischemic cardiomyopathy" may include cardiomyopathies due to volume or pressure overload, such as hypertension or valvular heart disease.

Classifications of cardiomyopathies (see Chap. 16) mixing anatomic designations (i.e., hypertrophic and dilated) with functional ones taking hemodynamic properties into consideration such as restrictive cardiomyopathies can be quite challenging and have failed to satisfy purposes of all users. Confusion may arise because the same disease could appear in two categories (i.e., hypertrophic and restrictive); there could be heterogeneity of clinical expression in different phenotypes and change from one category to another during their natural clinical course; e.g., amyloid and other infiltrative conditions may progress from a restrictive cardiomyopathy state to a dilated form. The most recent MOGE(S) classification (morphofunctional phenotype (M), organ(s) involvement (O), genetic inheritance pattern (G), etiological annotation (E) including genetic defect or underlying disease, and the functional status (S) of the disease) provides the flexibility of such potential transitions between morphofunctional types, involvement of different cardiac structures and organs, progression of symptomatology and functional status, and addition of different etiologies such as genetic defects that may be discovered through the lifetime of a patient or affected families [4].

1.3 Stages of HF According to Risk and Symptoms

The ACCF/AHA stages of HF emphasize the development and progression of disease and can be used to describe individuals and populations:

Stage A is defined as patients at high risk for HF but without structural heart disease or symptoms of HF.

Stage B is defined as patients with structural heart disease but without signs or symptoms of HF.

Stage C is for patients with structural heart disease with prior or current symptoms of HF.

Stage D is patients with refractory HF requiring specialized interventions [5] (Fig. 1.1).

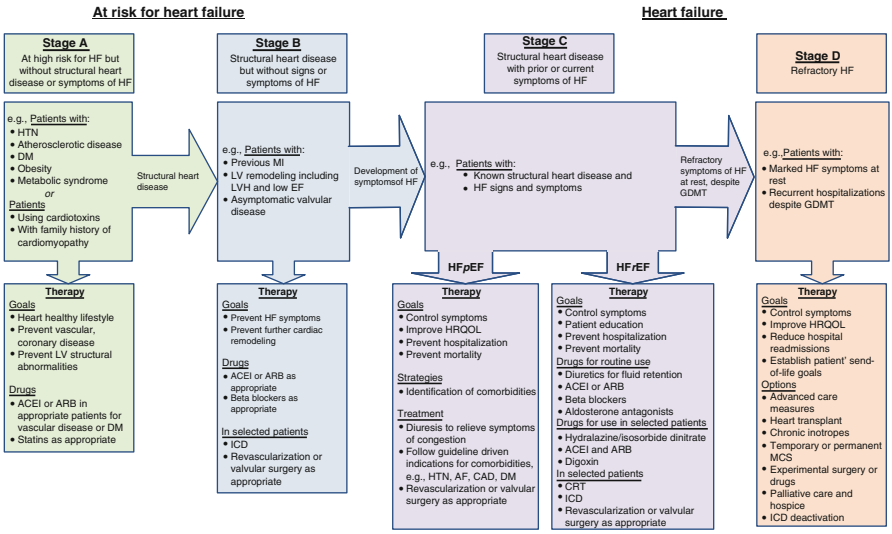

Fig. 1.1 ACCF/AHA stages of HF according to risk and symptoms (Reproduced with permission from *JACC* [5])

NYHA classes focus on exercise capacity and symptoms of HF (see Chap. 9):

NYHA class I patients with no limitation of physical activity and ordinary physical activity does not cause symptoms of HF

NYHA class II slight limitation of physical activity, comfortable at rest, but ordinary physical activity results in symptoms of HF

NYHA class III marked limitation of physical activity, with patient being comfortable at rest, but less than ordinary activity causes symptoms of HF

NYHA class IV patients who are unable to carry on any physical activity without symptoms of HF or symptoms of HF at rest

1.4 Evaluation of a HF Patient

Evaluation of a HF patient includes a thorough history and physical examination, ascertainment of symptoms, functional capacity, and volume status including ascertainment of dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, fatigue, and lower extremity edema. Etiology, comorbidities, and contributing factors for HF should be addressed including presence of diabetes; hypertension; smoking; prior cardiac disease; family history of cardiac disease, HF, or cardiomyopathy; history of heart murmur, congenital heart disease, and rheumatic fever; sleep disturbances; thyroid disease history; exposure to infectious etiology; exposure to cardiotoxins; and past or current use of alcohol and illicit drugs.

Pertinent physical examination includes heart rate and rhythm; blood pressure; measurements of weight, height, and body mass index; overall volume status;

Table 1.1 Initial diagnostic work-up of a HF patient

Detailed history	Detailed history for causes of HF, review of comorbidities, medications, social history, drug or substance use, cardiotoxin or infectious exposure, pregnancy. In patients with idiopathic DCM, a 3-generational family history should be obtained to aid in establishing the diagnosis of familial DCM
Initial diagnostic work-up	Complete blood count with differential
	Metabolic panel: serum electrolytes including glucose, calcium, magnesium, BUN, creatinine, HbA1c
	Urinalysis
	Thyroid function tests
	Liver function tests
	Chest radiography
	Echocardiography
	12-Lead electrocardiography
	Measurement of BNP or NT-proBNP to support clinical judgment for the diagnosis of acutely decompensated HF, especially in the setting of uncertainty for the diagnosis
	Screening for or HIV, hemochromatosis, rheumatologic diseases, amyloidosis, or pheochromocytoma in patients at risk or with clinical suspicion
Other testing that may be considered according to initial clinical assessment and further indications	Cardiac MRI to assess for myocardial infiltrative processes
	Cardiac catheterization for coronary or hemodynamic assessment
	Invasive hemodynamic monitoring with a pulmonary artery catheter to guide therapy in patients who have respiratory distress or clinical evidence of impaired perfusion in whom the adequacy or excess of intracardiac filling pressures cannot be determined from clinical assessment
	Ischemia and viability assessment in patients with ischemic heart disease
	Endomyocardial biopsy in patients presenting with HF when a specific diagnosis is suspected that would influence therapy
	Cardiopulmonary exercise testing to assess for functional capacity and or consideration for cardiac transplantation

jugular venous distension; carotid upstroke and presence/absence of bruits; lung examination for rales or effusions; cardiac examination for systolic or diastolic murmurs; displaced PMI (point of maximum impulse); presence of left ventricular heave; intensity of the second heart sound (S2); presence of third or fourth heart sound (S3 or S4); liver size; presence of ascites; presence of renal bruits; presence of abdominal aortic aneurysm; peripheral edema; peripheral pulses; checking whether the extremities are cold and clammy.

Initial laboratory evaluation of patients presenting with HF should include complete blood count, urinalysis, serum electrolytes (including calcium and magnesium), blood urea nitrogen, serum creatinine, glucose, fasting lipid profile, liver function tests, and thyroid-stimulating hormone [5]. Screening for hemochromatosis, human immunodeficiency virus (HIV), pheochromocytoma, amyloidosis, or rheumatologic diseases reasonable in selected patients, particularly if there is clinical suspicion for testing [5] (Table 1.1).

Initial cardiac evaluation includes a baseline electrocardiogram (ECG); chest X-ray; and a 2-dimensional echocardiogram with Doppler should be performed to

assess ventricular function, size, wall thickness, wall motion, and valve function [5] (Table 1.1). Cardiac magnetic resonance imaging is reasonable when assessing myocardial infiltrative processes or scar burden. Biomarkers, especially natriuretic peptides, are useful to support clinical decision making regarding the diagnosis of HF and establish prognosis both in chronic ambulatory or acutely decompensated/hospitalized HF patients [5]. Natriuretic peptide-guided HF therapy can be useful to achieve optimal dosing of guideline-directed medical therapy (GDMT) in select clinically euvolemic patients followed in a well-structured outpatient HF disease management program, while the usefulness of serial measurement of BNP or NT-proBNP to reduce hospitalization or mortality in patients with HF or the usefulness of BNP- or NT-proBNP-guided therapy for acutely decompensated HF is not well established. Cardiac troponins and other evolving biomarkers can be helpful with prognosis and risk stratification of HF patients (see Chaps. 10, 11, and 12).

1.5 Current Management Strategies in HF

1.5.1 Guideline-Directed Medical Therapy (GDMT)

The 2013 ACCF/AHA guideline for the management of HF provides a comprehensive guide to evaluation and management of HF patients [5]. Guideline-directed medical therapy (GDMT), which represents the optimal medical therapy recommended with a class I indication in patients with systolic HF, includes ACE inhibitors (ACE-I), angiotensin receptor blockers (ARBs) when ACE-I intolerant, β-blockers (specifically, bisoprolol, carvedilol, and extended-release metoprolol), and, in select patients, aldosterone receptor antagonists, hydralazine-nitrates, and diuretics as the mainstay of pharmacological therapy for HFrEF (Fig. 1.2) (see Chaps. 8, 36, 38, and 40). It should be noted that indications for aldosterone antagonists for symptomatic HFrEF patients include mild to moderate HF (NYHA class II) patients with a history of a prior cardiovascular hospitalization or elevated plasma natriuretic peptide levels. Additionally existing indications include NYHA class III and IV HF patients with severe HF [5] but with safeguards of creatinine ≤2.5 mg/dL in men or ≤2.0 mg/dL in women and potassium ≤5.0 mEq/L along with the necessity for careful monitoring of potassium, renal function, and diuretic dosing at initiation follow-up in patients treated with aldosterone antagonists. Routine combined use of an ACE inhibitor, ARB, and aldosterone antagonist is considered potentially harmful and is not recommended [5]. The combination of hydralazine and isosorbide dinitrate is recommended in African-American patients with NYHA class III–IV HFrEF and is considered potentially useful in patients who are ACE inhibitor or ARB intolerant. Digoxin similarly is potentially beneficial in patients with HFrEF to decrease hospitalizations for HF (remains a class IIa recommendation) [5].

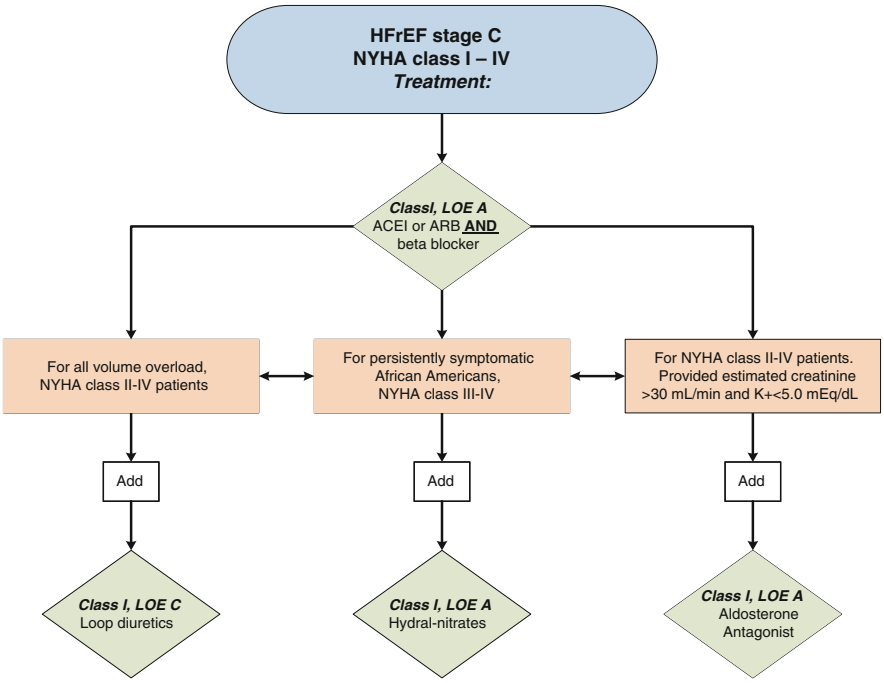

Fig. 1.2 Evidence-based, guideline-directed medical therapy in symptomatic stage C (NYHA class I–IV) HF patients with reduced ejection fraction (HFrEF) (Reproduced with permission from *JACC* [5])

1.5.2 Device Therapy

Implantable cardioverter defibrillator (ICD) is recommended for primary prevention of sudden cardiac death in selected patients with LVEF ≤35 % and NYHA class II or III symptoms, who have reasonable expectation of meaningful survival for more than 1 year [5] (Chap. 8).

Cardiac resynchronization therapy (CRT) is recommended in patients who have LVEF ≤35 %, sinus rhythm, left bundle branch block (LBBB) with a QRS duration of ≥150 ms, and NYHA class II, III, or ambulatory IV symptoms on GDMT. CRT can be useful in patients with LBBB but QRS duration of only 120–149 ms or those with non-LBBB pattern and QRS ≥150 ms. Of note, for patients with non-LBBB and QRS 120–149 ms, the CRT indication is not expanded beyond patients with NYHA class III/ambulatory class IV; and in patients with non-LBBB and QRS <150 ms and with NYHA class I or II symptoms, CRT or ICD is not indicated in patients in whom cardiac or noncardiac comorbidity and/or frailty limit survival with good functional capacity to less than 1 year [5].

Mechanical circulatory support (MCS) can be considered in select advanced HF patients in whom definitive management such as cardiac transplantation is planned

(i.e., as a "bridge to transplant"); or cardiac recovery is anticipated (i.e., as a "bridge to recovery"), or as "destination therapy." Nondurable MCS, including the use of percutaneous and extracorporeal ventricular assist devices, is considered reasonable as a "bridge to recovery" or a "bridge to decision" for carefully selected patients with acute, profound hemodynamic compromise. These considerations are in line with the current patient care spectrum, reflecting a higher and broader use of these devices in different clinical scenarios [5].

1.5.3 Acute Decompensated HF

In acute decompensated hospitalized HF patients, intravenous loop diuretics such as furosemide, torsemide, and bumetanide remain as first-line therapy. When diuresis is inadequate, it to be reasonable to intensify the diuretic regimen using either higher doses of intravenous loop diuretics or adding a second (e.g., thiazide) diuretic. In the absence of hypotension, intravenous vasodilators such as nitroglycerin, nitroprusside, or nesiritide may be considered as an adjunct to diuretic therapy for relief of dyspnea in patients admitted with acutely decompensated HF [5].

1.6 Emerging Therapies in HF

Some of the emerging therapies in HF are reviewed below, and strategies such as gene therapy and microRNA therapeutic are also discussed at length in Chap. 14 and 15.

1.6.1 Cardiac Inotropes

Currently used inotropic agents have failed to show benefit beyond short-term hemodynamic improvements in patients with HF [6]. These include cardiac glycosides, β-adrenoceptor agonists, phosphodiesterase (PDE) inhibitors, and calcium sensitizers. Heightened energy utilization and the coupling of contractility, chronotropy, and calcium represent significant limitations to their use. Not only do they induce maladaptive remodeling by increasing metabolic demands on the heart, they are also pro-arrhythmic. Increased arrhythmias associated with their use increase mortality and morbidity in patients with decompensated HF. Two novel therapies attempting to dissociate inotropy and arrhythmogenicity are cardiac myosin activators such as omecamtiv mecarbil and istaroxime.

Cardiac myosin activators (CMA) are drugs that directly target the force-generating cardiac enzyme and myocardial myosin ATPase, accelerating its activity in order to enhance contractility. They increase cardiac myosin ATPase, enhancing the release of inorganic phosphate, which strengthens binding between myosin and actin, leading to shortening of the cardiac sarcomere. CMAs increase the efficiency

with which ATP is utilized without increasing ATP consumption by increasing the number and duration of actin-myosin crossbridges for each ATP molecule consumed. This prolongs systole but not the rate at which force is developed. This is unlike conventional inotropic agents that generally increase ATP consumption and increase the velocity of contraction and rate of force generation but may shorten the duration of systole. Importantly, CMAs do not possess phosphodiesterase activity, do not increase diastolic calcium concentrations, and can increase cardiac performance in patients receiving beta-blockers. In the phase II Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute HF (ATOMIC-AHF) study, omecamtiv mecarbil did not achieve its primary efficacy endpoint in reducing dyspnea in patients with acute HF. However, a cohort which received the highest dose of the drug showed greater dyspnea relief compared with placebo. *C*hronic *O*ral *S*tudy of *M*yosin Activation to *I*ncrease *C*ontractility in *HF* (COSMIC-HF) is a double-blind, randomized, placebo-controlled, multicenter, dose escalation study designed to assess the pharmacokinetics and tolerability of three oral modified-release formulations of omecamtiv mecarbil in patients with chronic HF and left ventricular systolic dysfunction. Calcium dynamics play a prominent role in cardiac function, and its abnormalities contribute to several cardiac diseases including HF, which is discussed at length in Chap. 4.

Istaroxime, an inhibitor of Na^+/K^+-ATPase and an activator of sarcoplasmic reticulum calcium pump (SERCA), is a new luso-inotropic compound that stimulates cardiac contractility and relaxation in healthy and failing hearts in animal models and in patients with acute HF syndrome. The HORIZON-HF trial evaluated the hemodynamic, echocardiographic, and neurohormonal effects of intravenous istaroxime in 120 patients hospitalized with HF and reduced ejection fraction. In this randomized, double-blind, placebo-controlled, dose-escalating study, three doses of istaroxime or a placebo were given as intravenous infusions over 6 h to patients with a history of HF and a pulmonary capillary wedge pressure (PCWP) over 20 mmHg [7]. A reduction in PCWP was the primary endpoint, which was attained in all three dose groups during the entire observation period of 6 h. There was an increase in systolic blood pressure and a transient increase in cardiac index with the highest dose and a decrease in heart rate and diastolic and systolic volume, without a change in ejection fraction. Echocardiographic indicators of diastolic function also showed improvement. The limitation of this study is related to the fact that patients included presented with milder forms of acute HF, not requiring inotropic interventions.

Research involving gene therapy approaches to increase sarcoplasmic reticulum calcium pump activity and is also ongoing (Chap. 15).

1.6.2 Neurohormonal Modulation

The renin-angiotensin aldosterone system (RAAS) represents a long established therapeutic target in cardiovascular disease, and multiple inhibitors of the pathway have been shown to improve outcomes in chronic HF. However, the inhibition of downstream pathway activity can produce a compensatory rise in plasma renin

activity that can competitively overcome RAAS blockade. Hence, aliskiren, a direct renin inhibitor, was studied in the Aliskiren Trial on Acute HF Outcomes (ASTRONAUT) [8]. This international, double-blind study enrolled stable patients hospitalized for HF and followed them after discharge. Patients were randomized to receive either aliskiren, starting at 150 mg and increasing to 300 mg, or placebo, in addition to other standard HF therapies. After 6 months, patients in both groups had a similar likelihood of cardiovascular death or rehospitalization for HF. Despite a significant and sustained reduction in natriuretic peptide level, aliskiren did not reduce mortality or rehospitalization rates. It is possible that a beneficial effect on HF progression, as suggested by this long-term improvement in natriuretic peptide level, was offset by potential negative drug-associated effects, such as hyperkalemia, hypotension, and worsening renal function, particularly in patients with diabetes mellitus (Chap. 36).

More recently, the results of the PARADIGM-HF trial were presented at the European Society of Cardiology meeting where the angiotensin receptor neprilysin inhibitor LCZ696 was superior to enalapril in reducing the risk of death and of hospitalization for HF [9]. Neprilysin, a neutral endopeptidase, degrades several endogenous vasoactive peptides, including natriuretic peptides, bradykinin, and adrenomedullin. Inhibition of neprilysin increases the levels of these substances, countering the neurohormonal overactivation that contributes to vasoconstriction, sodium retention, and maladaptive remodeling. Combined inhibition of the renin-angiotensin system and neprilysin had effects that were superior to those of either approach alone in experimental studies, but in clinical trials, the combined inhibition of ACE and neprilysin was associated with serious angioedema. LCZ696, which consists of the neprilysin inhibitor sacubitril (AHU377) and the ARB valsartan, was designed to minimize the risk of serious angioedema.

1.6.3 Autonomic Nervous System Modulation in HF

The pathophysiology of HF is characterized by neurohormonal activation and autonomic imbalance with increase in sympathetic activity and withdrawal of vagal activity. In the failing human heart, increased sympathetic outflow from the central nervous system in HF affects several key organs, including the heart, the kidney, and the peripheral vasculature. In the acute setting, catecholamine-induced augmentation of ventricular contractility and heart rate helps maintain cardiac output. Increased sympathetic activity also leads to systemic vasoconstriction and enhanced venous tone, both of which initially contribute to maintenance of blood pressure. Both norepinephrine and angiotensin II stimulate proximal tubular sodium reabsorption, which contributes to sodium retention and volume expansion characteristic of HF. The heart responds to the increase in venous return with an elevation in end-diastolic volume that results in a rise in stroke volume via the *Frank–Starling* mechanism. However, chronic sympathetic stimulation causes detrimental effects on the heart like interstitial growth and remodeling that increase myocardial mass

and may lead to further enlargement of the left ventricular chamber [10]. The elevated sympathetic nervous system (SNS) outflow and norepinephrine in chronic HF lead to chronically elevated stimulation of the cardiac β-adrenergic receptor system. In an attempt to defend the heart against excessive catecholaminergic toxicity, the body responds by downregulating β1-adrenergic receptors and causes G-protein-coupled receptor kinases (GRK2)-mediated cardiac β1-adrenergic receptor and β2-adrenergic receptor desensitization. This results in a reduction in cardiac β-adrenergic receptor density and responsiveness and resulting in cardiac inotropic reserve depletion. The pathophysiology of HF is discussed in detail in Chap. 3.

1.6.4 Novel Sympathetic Nervous System Modulation Drugs

Clinical trials clearly demonstrate a strong association between increased heart rate increased mortality and morbidity in patients with a wide spectrum of cardiac diseases including CAD and HF. Heart rate reduction has in part been shown to contribute to the beneficial effects of beta-blockers in HF (Chap. 5). Post hoc analysis of the CIBIS II trial showed that baseline heart rate and heart rate change on beta-blocker, bisoprolol, are significantly related to prognosis in HF [11]. The lowest baseline heart rate and the greatest heart rate change were associated with best survival and reduction of hospital admissions. Heart rate is currently not the determining factor when uptitrating β-blockers in HF. In the major guidelines, the emphasis has been on trying to achieve the target doses used in the major clinical trials. In these trials, β-blocker dose was not determined by heart rate effects, but by a prespecified "target" dose or limiting symptoms. The use of beta-blockers in patients with HF is limited by hypotension and symptoms which precludes upward titration of the dose to the "target dose."

Ivabradine, a novel medication, is a selective inhibitor of the hyperpolarization-activated cyclic-nucleotide-gated *funny* current (I_f) involved in pacemaking generation and responsiveness of the sinoatrial node, which results in heart rate reduction with no other apparent direct cardiovascular effects. The Systolic Heart Failure Treatment with the I_f Inhibitor Ivabradine Trial (SHIFT) investigated the effect of heart rate reduction using the selective sinus node inhibitor ivabradine on outcomes in HF. A total of 6,558 patients with HF, a left ventricular ejection fraction ≤35 %, and a sinus heart rate of ≥70 beats per minute were randomly assigned to ivabradine or placebo and followed for a median of 23 months [12]. The primary endpoint was a composite of cardiovascular death or hospital admission for worsening HF. Patients in the ivabradine group experienced the primary endpoint less frequently than those in the placebo group (24 vs. 29 %) largely due to reduced hospitalizations for HF (HR 0.74, 95 % CI 0.66–0.83) and reduced deaths due to HF (HR 0.74, 95 % CI, 0.58–0.94). Patients in the ivabradine group with an achieved heart rate less than 60 bpm at 28 days had fewer primary endpoint events than those with higher heart rates. Based on the results of the SHIFT, the European Society of Cardiology (ESC) guidelines in 2012 recommended that ivabradine should be considered to reduce the

risk of heart failure hospitalizations in patients in sinus rhythm (SR), LVEF ≤35 %, an HR ≥70 bpm, and persisting symptoms (NYHA class II–IV) despite treatment with an evidence-based dose of β-blocker, ACE-I, and an aldosterone receptor antagonist (class of recommendation/level of evidence: IIa/B). Also it may be considered to reduce the risk of HF hospitalization in patients in SR with an EF ≤35 % and an HR ≥70 bpm, who are unable to tolerate a β-blocker (COR/level of evidence: IIb-C). However, a limitation of the SHIFT is that only 23 % of patients were receiving target doses of beta-blockers. Patients receiving 50 % or more of target β-blocker doses at baseline had no significant benefit from ivabradine for the primary endpoint. Also the mechanism of benefit of ivabradine is not completely clear. HR reduction might be part of the benefit, but ivabradine also has other effects, e.g., on calcium handling which might affect ventricular remodeling and contribute to the beneficial effect of the drug. From the available data, ivabradine might reduce heart failure hospitalizations when added to contemporary heart failure therapies. It remains unknown whether ivabradine can improve outcomes in addition to optimally managed heart failure therapies or its benefits relative to other therapies, especially β-blockers. The results from SHIFT provide the basis for additional trials to test these important and clinically relevant questions.

1.6.4.1 Vagal Nerve Stimulation

Reduced vagal activity is associated with increased mortality in patients with HF, and many investigators have shown that restoration of autonomic regulatory function by vagal nerve stimulation improves survival in animal models of HF [13]. A multicenter, open-label phase II safety and feasibility study was reported with the use of right cervical vagal nerve stimulation synchronized to the cardiac cycle (Cardiofit System, BioControl Medical, Yehud, Israel), which showed that chronic vagal nerve stimulation may be safe and tolerable and may improve quality of life and LV function [14]. This was followed by a feasibility study, the Autonomic Neural Regulation Therapy to Enhance Myocardial Function in Heart Failure (ANTHEM-HF) study [15], which used the Cyberonics vagal nerve stimulation therapy system and provides additional information on the role of autonomic regulation therapy in patients with LV dysfunction and chronic symptomatic HF. In this study, subjects were randomized to thoracic subcutaneous vagal nerve stimulation (VNS) therapy system implantation for either right or left cervical VNS. Following titration, VNS was then delivered for 6 months at an amplitude of 2.0 (±0.6) mA and a constant frequency of 10 Hz.

The study showed significant improvement (mean 4.5 %) from baseline in left ventricular ejection fraction (LVEF) among all patients, with no statistically significant differences between left- and right-sided VNS. There was also a mean improvement of 56 m in the 6-minute walk test, but this improvement was significantly less with left- compared to right-sided VNS. There was a similar rate of device-related adverse events in both groups, including transient mild dysphonia (voice alteration), cough, and oropharyngeal pain, which resolved during the study. These results are promising and need to be confirmed in a larger, controlled trial (Chap. 6).

1.7 Advances in Devices in HF

In the last 15–20 years, the treatment of HF has expanded with the addition of implantable devices to the standard pharmacotherapy. Devices continue to evolve and change with each new generation that is produced. With their changes in design, function, and the addition of cardiac monitoring abilities, the devices are beginning to be studied at earlier stages of HF emphasizing the importance of consideration of device therapy as one would consider pharmacotherapy in their patients (Chap. 8).

Despite the benefits of CRT, about 25–30 % of HF patients with proper indications for CRT are nonresponders and do not have clinical benefit or echocardiographic evidence of improvement in ventricular dyssynchrony. This is mostly due to ineffective placement of the left ventricular lead [16]. In an attempt to improve left ventricular pacing, CRT devices were made with quadripolar left ventricular leads as opposed to the standard bipolar left ventricular lead. This allows for more pacing options proximally along the left ventricular lead in order to tailor therapy for the individual patient. There has been some echocardiographic evidence of improved ventricular synchrony, but no studies have compared bipolar to quadripolar CRT devices for clinical benefit [17]. The technical difficulties of placing endovascular leads in the coronary sinus were also thought to contribute to suboptimal lead placement; therefore, epicardial leads have been developed. Despite this, no clinical benefit has been demonstrated with epicardial leads as opposed to endovascular [18]. Also being developed are leadless CRT devices in which endocardial electrodes are placed and a wireless transmitter is implanted subcutaneously [19]. The wireless transmitter sends ultrasound signals to the endocardial electrodes which then electrically pace. Eliminating the need for leads allows one to place the pacing electrode almost anywhere in the heart, and it is not dependent on the anatomy of the coronary sinus. Another emerging area of improvement for nonresponders is automatic optimization of atrioventricular (AV) and interventricular (VV) delay by the device itself. The RESPOND-CRT trial is evaluating for safety and clinical benefit of a device that automatically reprograms the AV and VV delay weekly according to vibration sensing of the right atrial lead that is a surrogate for contractility [20].

Additional cardiac monitoring abilities of implantable devices include impedance measurements to assess for increasing volume overload. Right ventricular lead impedance monitoring was unable to show clinical benefit due to the high rate of false positives, but early evaluation of using the left ventricular lead in CRT devices has shown greater specificity, thus decreasing the amount of false positives [21, 22]. The clinical benefit is yet to be established, but some recent studies have shown that telemonitoring of cardiac parameters by intracardiac devices results in decreases in composite outcomes of death, hospitalizations, and change in NYHA class [23]. Further trials are needed to evaluate the clinical effectiveness or use of these newer CRT devices with monitoring capabilities.

Clinical trials demonstrating benefit of ICDs were performed with single-chamber ICDs. Dual-chamber ICDs help in the identification of atrial rhythms, but there is controversy over whether the increased cost justifies the identification. Also it is controversial, and studies conflict on the ability of dual-chamber ICDs to reduce

unnecessary shocks by their identification of atrial rhythms. In the ICD subset of the MADIT-CRT trial, unnecessary shocks were not significantly different in single-chamber versus dual-chamber devices [24]. As with CRT, trials have evaluated the clinical effectiveness of ICDs that have the ability to perform HF parameter monitoring. Impedance testing to look for pulmonary fluid overload has shown decreases in hospitalizations by identifying worsening volume overload sooner [25]. Going even farther than impedance testing was the HOMEOSTASIS trial which was the first to test a septal anchoring device with ICDs that directly measures left atrial pressure [26]. This measurement combined with a physician-directed patient self-management program resulted in decreased hospitalizations and mortality. Newer methods of placing ICDs subcutaneously, as opposed to endovascular, have not changed outcomes but allow for better options in select patients, such as those with history of device infection and end-stage renal disease patients needing venous dialysis access [27].

Patients who continue to have worsening hemodynamics and HF despite pharmacologic and implantable device therapy mentioned above are considered for transplant and ventricular assist devices. The growing population of advanced HF patients and limited availability of donor hearts creates an increasing number of patients with left ventricular assist devices (LVADs). LVADs were initially intended for bridge to transplant, but with continued use and development of smaller, more durable devices are being increasingly used as "destination therapy" [28]. LVADs are also being used as "bridge to recovery" and are able to be explanted in patient's that recover enough heart function to be managed solely by pharmacologic agents [29]. First-generation LVADs (Novacor and HeartMate XVE) worked by pulsatile flow, but second-generation (HeartMate II and Jarvik 2000) and third-generation (HeartMate HVAD) LVADs have moved to continuous flow pumps that allow for smaller pumps with higher flow rates [30]. Most models consist of an inflow tract that draws blood out of the left ventricle into the pump which then sends blood to the outflow tract typically attaching to the aorta. The second-generation pumps have to sit in the abdominal cavity due to their size, but some of the emerging smaller third-generation pumps reside within the pericardium. LVADs allow for ventricular unloading which is thought be a significant contributor to reverse remodeling that allows for either bridge to recovery or bridge to candidacy for transplant by improving hemodynamics and perfusion of other affected organs [30–32]. The major complications associated with current LVADs include infection, stroke, and gastrointestinal bleeding.

Emerging therapies include percutaneously placed ventricular assist devices which include the Impella LP2.5, TandemHeart, and Reitan catheter pump [33]. The advantages of these pumps are that they can be placed quickly in the catheter lab for patients with acute cardiogenic shock and removed easily once the acute event is over. The disadvantage is that they should not stay in place for long periods of time for patients who do not recover. These percutaneous LVADs are increasingly being used for patients with HF but not acutely decompensated undergoing high-risk percutaneous coronary intervention (PCI). The Impella is a catheter-based system that uses an impeller-driven continuous flow pump which delivers blood from

the left ventricle to the aorta with up to 2.5 L/min of cardiac output. The TandemHeart is a left atrial to femoral artery bypass system that uses a continuous flow centrifugal pump to deliver up to 5.0 L/min of cardiac output. The Reitan catheter pump is placed in the proximal descending aorta and uses a propeller pump to create a gradient in the aorta thereby decreasing afterload.

Still being studied in ongoing trials are micropumps that are percutaneous ventricular assist devices designed to be placed in patients with NYHA class IIIb or IV HF [34, 35]. They are meant for patients to be able to wear in the ambulatory setting just as the first-, second-, and third-generation LVADs mentioned above, but they do not produce as much cardiac output with peak flow around 2.5–3.0 L/min. The micropumps are inserted underneath the skin much like an ICD generator and then have inflow catheter that is transseptal to draw blood from the left atrium. The outflow catheter then delivers blood to the subclavian. The clinical benefit with micropumps is being evaluated with further trials.

1.8 Exercise in HF

A number of studies have demonstrated the need of small amounts of exercise for patients with HF. This is being discussed at length in Chap. 9.

1.9 Care Coordination, Transitions of Care, and Shared Decision Making

Clinicians must maintain vigilance about psychosocial, behavioral, and socioeconomic issues that patients with HF and their caregivers face, including access to care, risk of depression, and healthcare disparities. Every patient with HF should have a clear, detailed, and evidence-based plan of care that ensures the achievement of GDMT goals, effective management of comorbid conditions, timely follow-up with the healthcare team, appropriate dietary and physical activities, and compliance with guidelines [5]. This plan of care should be updated regularly and made readily available to all members of each patient's healthcare team.

Effective systems of care coordination with special attention to care transitions should be deployed for every patient with chronic HF that facilitate and ensure effective care that is designed to achieve GDMT and prevent hospitalization. This may include communication between primary care physicians, hospitalists, HF specialists, family, patient, nurses, nurse practitioners, clinical pharmacists, and physician assistants.

Improved communication between clinicians and nurses, medication reconciliation, carefully planned transitions between care settings, and consistent documentation are examples of patient safety standards that should be ensured for all patients with HF [5].

Palliative and supportive care is effective for patients with symptomatic advanced HF to improve quality of life [5]. The HF team should help patients and their families explore treatment options and prognosis, with emphasis on patient's goals and preferences, especially for advanced HF patients who require frequent hospitalizations and who remain refractory despite advanced therapies. Along with above strategies, patients with HF should receive specific education to facilitate HF self-care and shared decision making [5].

1.10 Concluding Remarks

HF is a very prevalent medical condition with significant mortality and morbidity. In the last two decades, our understanding of etiology, definition, classification, diagnosis, and treatment of heart failure has significantly evolved, but HF still remains as the leading cause of hospitalizations among elderly patients and approximately half of the people who develop HF will die within 5 years of diagnosis. Development of patient centric care delivery models, new medical and device therapies, and enhancement of care coordination will likely improve clinical outcomes and patient quality of life.

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