Treatment of Heart Failure: An Update

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Faculty

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Audience

This course is designed for nurses and ancillary nurse personnel involved in the treatment and continued assessment of patients with heart failure.

Accreditations & Approvals

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About the Sponsor

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Course Objective

The purpose of this course is to provide nurses and ancillary nursing personnel with current information about the scientific advances in the treatment of acute heart failure.

Learning Objectives

Upon completion of this course, you should be able to:

1. Summarize the incidence and financial impact of heart failure.

2. Identify the four stages of heart failure.

3. Discuss the neurohormonal components of heart failure.

4. Describe the role of B-type natriuretic peptide (BNP) in the diagnosis of heart failure.

5. Define the role of vasoactive systems in the pathogenesis of heart failure.

6. Review the use of BNP as a point-of-care testing tool and in guiding therapy of heart failure in the outpatient setting.

7. Outline the management of patients with symptomatic and asymptomatic heart failure.

8. List devices used in the management of heart failure.

9. Describe impedance cardiography as a noninvasive tool to assess cardiovascular status of patients with heart failure.

10. Discuss the role of members of the multidisciplinary team in the heart failure clinic.

11. Outline the treatment plan of those patients enrolled in the heart failure clinic.

12. Discuss the future directions in the treatment of heart failure.

13. Summarize the Joint Commission guidelines for heart failure-specific care.

EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Heart failure represents a major public health concern, with an increasing prevalence in developed countries [1]. In the United States alone, approximately 6 million people 20 years of age and older suffer from heart failure [2]. The clinical syndrome of heart failure is the final pathway for a myriad of diseases that affect the heart. The economic and psychosocial impact heart failure has on society is phenomenal. The incidence, prevalence, morbidity, and mortality of heart failure have become an epidemiologic nightmare for the healthcare system. The incidence of heart failure has increased as treatment for previously fatal ischemic, structural, and inflammatory cardiovascular conditions have improved and as the bulk of the U.S. population ages. Concomitantly, the proportion of the healthcare economy spent on the diagnosis, treatment, and chronic management of heart failure has increased dramatically, demanding even greater efforts to respond to this condition. Despite advances in treatment, patients admitted with decompensated heart failure have significant mortality and early readmission rates (i.e., rehospitalization within 60 days) [3].

INCIDENCE OF HEART FAILURE

Heart failure is a frequent cause of hospitalization and mortality, with 809,000 hospital discharges each year, including more than 83,000 deaths among individuals 20 years of age and older [2]. Heart failure occurs in 21 per 1,000 individuals 65 years of age and older, with more than 900,000 new cases diagnosed annually. After 80 years of age, the prevalence of heart failure in women (11.0%) exceeds that of men (9.5%) due to longer life expectancy. The overall prevalence of heart failure is projected to increase 46% between the years 2012 to 2030, in part because of current therapies for cardiac disorders, such as myocardial infarction, valvular disease, and arrhythmias, are allowing patients to survive longer [2].

As noted, heart failure is a leading cause of hospitalizations among patients 20 years of age and older [2]. Heart disease is the third most common reason for hospital admissions among persons older than 65 years of age [4]. Community surveillance data from 2005 to 2014 indicate that rates of hospitalizations for heart failure are increasing over time [2]. The in-hospital mortality rate for acute decompensated heart failure (ADHF) is 5% to 8% [3]. Patients with ADHF face a median six-day duration of hospitalization, and the rehospitalization rate in the two months and six months following discharge as high as 20% and 50%, respectively [3; 5]. Survival after the onset of heart failure in older adults has improved; however, improvements are not even across all demographics. Among Medicare beneficiaries, the overall one-year mortality rate declined slightly from 1998 to 2008 but remained high at 29.6%. According to a study conducted by the National Heart, Lung, and Blood Institute (NHLBI), the 30-day, one-year, and five-year case fatality rates after hospitalization for heart failure were 10.4%, 22.0%, and 42.3%, respectively [2]. Racial and ethnic disparities in death resulting from heart failure persist, with non-Hispanic Black patients having the highest death rate per capita. A report examining the U.S. population found age-adjusted mortality rate for heart failure to be 92 per 100,000 individuals for non-Hispanic Black patients, 87 per 100,000 for non-Hispanic White patients, and 53 per 100,000 for Hispanic patients [6].

The estimated annual cost of heart failure in the United States, including direct and indirect costs, totals $31 billion; however, by 2030 the total cost of heart failure is projected to increase to nearly $70 billion [2]. Ambulatory care, which includes emergency room visits, takes its toll of nearly $14.7 billion a year, and heart transplantation involves expenditures of less than $30 million annually [7]. Ambulatory patients with persistent Class IV symptoms have a one-year mortality rate that approaches 50%. Those who can maintain relief from congestion regain a prognosis similar to that of Class II patients, with a one-year mortality of approximately 20% to 25%. Emergency department visits and

subsequent hospitalizations for ADHF continue to constitute a major public health burden, with hospitalizations for heart failure having increased from 577,000 in 1985 to more than 1 million in 2010 in the United States [8; 9].

STAGES OF HEART FAILURE

Although heart failure is a major public health problem, there are no national screening efforts to detect the disease at its earlier stages, as there are for breast and prostate cancer or osteoporosis. The guidelines for the evaluation and management of heart failure, published in 2013 by the American College of Cardiology Foundation and the American Heart Association (ACCF/AHA), and updated in 2017 and 2022 by the American College of Cardiology, the AHA, and the Heart Failure Society of America (ACC/AHA/HFSA), have defined the factors that render a patient at high risk for heart failure [10]. These guidelines are based on a classification of heart failure with emphasis on its evolution and progression, known as the four stages of heart failure. Patients with Stage A heart failure are at high risk for the development of heart failure but have no apparent structural abnormality of the heart. Patients with Stage B heart failure (pre-heart failure) have a structural abnormality of the heart but have never had symptoms of heart failure. Patients with Stage C heart failure have a structural abnormality of the heart and current or previous symptoms of heart failure. Patients with Stage D heart failure have end-stage symptoms of heart failure that are refractory to standard treatment [10; 11]. This staged classification underscores the fact that established risk factors and structural abnormalities are necessary for the development of heart failure. This system is a departure from the traditional New York Heart Association (NYHA) classification, which has primarily been used as a shorthand to describe functional limitations of patients with Stage C or Stage D heart failure. Patients with Stage C heart failure can be classified according to the trajectory of their symptoms [10; 12]. The NYHA classes are [10]:

- Class I: Patients with cardiac disease but resulting in no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.

- Class II: Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.

- Class III: Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.

- Class IV: Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.

The two systems are often used in conjunction to better describe the severity of the disease.

The 2022 AHA/ACC HFSA guideline for the management of heart failure additionally considers left ventricular ejection fraction (LVEF) important in the classification of patients with heart failure because most clinical trials select patients based on their ejection fraction (***Table 1***) [10].

Heart failure with preserved ejection fraction (HFpEF) represents at least 50% of the population with heart failure, and its prevalence is increasing. It has been variably classified as LVEF > 40%, > 45%, or ≥ 50%. Because some of these patients do not have entirely normal LVEF but also do not have a major reduction in systolic function, the term "preserved EF" is used. In the 2022 AHA/ACC HFSA guideline, the threshold for HFpEF is LVEF ≥ 50% [10]. Patients with heart failure and an LVEF between reduced (HFrEF) and preserved range have been termed as "heart failure with mid-range EF" or "heart failure with mildly reduced EF." Patients with heart failure with mildly reduced EF (HFmrEF) are

CLASSIFICATION OF HEART FAILURE BY LEFT VENTRICULAR EJECTION FRACTION	
Type of HF According to LVEF	**Criteria**
HF with reduced EF (HFrEF)	LVEF ≤40%
HF with improved EF (HFimpEF)	Previous LVEF ≤40% and a follow-up measurement of LVEF 40%
HF with mildly reduced EF (HFmrEF)	LVEF 41% to 49% Evidence of spontaneous or provokable increased LV filling pressures[a] (e.g., elevated natriuretic peptide)
HF with preserved EF (HFpEF)	LVEF ≥50% Evidence of spontaneous or provokable increased LV filling pressures[a] (e.g., elevated natriuretic peptide)
[a]Evidence for increased filling pressures can be obtained from noninvasive (e.g., natriuretic peptide, diastolic function on imaging) or invasive testing (e.g., hemodynamic measurements). HF = heart failure; LVEF = left ventricular ejection fraction; EF = ejection fraction; LV = left ventricular.	
Source: [10]	*Table 1*

usually in a dynamic trajectory to improvement from or deterioration to HFrEF. Therefore, one ejection fraction measurement at one time point may not be adequate. Trajectory of LVEF can be important, and a significant reduction in LVEF over time is a poor prognostic factor [10].

ETIOLOGY

In the United States, approximately 115 million people have hypertension, 100 million have obesity, 92 million have prediabetes, 26 million have diabetes, and 125 million have atherosclerotic cardiovascular disease [2]. These are known risk factors with high relative risk and population attributable risk for development of heart failure. Therefore, a large proportion of the U.S. population can be categorized as being at-risk for heart failure or for stage A heart failure. Based on population-attributable risks, hypertension has the greatest impact on the development of heart failure, accounting for 39% of heart failure events in men and 59% in women [13; 14]. In a 2016 retrospective study, more than 90% of patients with ADHF had hypertension, regardless of early readmission or no early readmission [3].

Despite its much lower prevalence in the population (3% to 10%), myocardial infarction also has a high attributable risk in men (34%) and women (13%) with heart failure. Although valvular heart disease accounts for only 7% to 8%, these patients should be managed in a multidisciplinary manner in accordance with clinical practice guidelines to prevent worsening of heart failure and adverse clinical outcomes [10]. Dyslipidemia, characterized by a high total high-density lipoprotein cholesterol ratio but a normal or low total cholesterol level, is also a risk factor for the development of heart failure. Findings from the Framingham Study suggest that obesity is a risk factor for the development of heart failure in men and women [13].

In 20% to 30% of the cases of heart failure with a depressed ejection fraction, the exact etiologic basis is not known. These patients are referred to as having nonischemic, dilated, or idiopathic cardiomyopathy if the cause is unknown. Prior viral infection or toxin exposure, alcohol use, or treatment with chemotherapeutic agents may also lead to a dilated cardiomyopathy. Although excessive alcohol consumption can promote cardiomyopathy, alcohol consumption is not associated with increased risk of heart failure and may protect against the development of heart failure when consumed in moderation [15].

The association between a low hemoglobin/hematocrit and adverse heart failure outcomes has also been recognized. Published estimates of the prevalence of anemia in patients with heart failure vary widely, ranging from 4% to 50% depending on the population studies and definition of anemia that is used. The severity of anemia may contribute to the increasing severity of heart failure. In the Framingham Study, a lower hematocrit was a significant risk factor for the development of symptomatic heart failure [16]. Given the risks and costs of red blood cell transfusion and the unclear benefit in patients with heart failure, the routine use of blood transfusion cannot be recommended for treating anemia that occurs in patients with stable heart failure [17]. Several small studies have suggested benefit from the use of erythropoietin analogs and/or iron for treatment of mild anemia in heart failure. However, there is concern that thromboembolic events may be increased with the former strategy. Treatment of anemia in patients with heart failure with the erythropoietin analog darbepoetin alpha was investigated in the large (2,278 participants) international study Reduction of Events with Darbepoetin in Heart Failure (RED-HF) [18]. While anemia did improve in the treatment group, there was no improvement in the rate of heart failure events, and more patients had fatal or nonfatal strokes in the darbepoetin alpha group (3.7%) than in the placebo group (2.7%) [18]. Overall, thromboembolic events occurred more frequently in the treatment group (13.5%) than in the placebo group (10.0%). Authors of the study concluded that treatment with darbepoetin alpha cannot be recommended.

NEUROHORMONAL COMPONENTS IN HEART FAILURE

Several neurohormonal changes, including a raised catecholamine level, overactivity of the renin-angiotensin-aldosterone system (RAAS), and elevation of natriuretic peptides, occur when heart failure becomes chronic. These changes are related to an increased mortality rate in patients with heart failure. Initially, these systems are thought to have compensatory effects, but eventually they contribute to increased vascular resistance and ventricular remodeling. According to the neurohormonal hypothesis, heart failure progresses due to the deleterious effects of the activated endogenous neurohormonal system on the heart and circulation. Both norepinephrine and epinephrine can cause an increased metabolic rate, with levels being markedly raised in patients with heart failure and cardiac cachexia. Additionally, cortisol and aldosterone plasma levels, as well as plasma renin activity, are particularly elevated in patients with cardiac cachexia, suggesting a specific association between the development of body wasting and the presence of neurohormonal activation in heart failure [19].

Increased knowledge about the pathophysiology of heart failure has resulted in significant advances in the management of the disease. In the past, heart failure was considered solely a hemodynamic problem caused by a weak pump, resulting in symptoms of pulmonary congestion and fatigue. Since then, the significance of neurohormonal changes occurring in patients with heart failure has received much more attention. Research has focused on the activation of the renin-angiotensin and sympathetic nervous systems in heart failure. Activation of one system will in turn activate the other, and both systems cause heart failure to worsen. In addition, the left ventricle can undergo changes, referred to as remodeling, that result in the progression of heart failure [20].

Following myocardial injury, the inciting event in heart failure involves adaptation of the cardiac myocyte to increased wall stress in order to maintain an adequate cardiac output. The primary myocardial response includes myocyte hypertrophy and remodeling, usually of the eccentric type. Although the hypertrophic state is induced by mechanical distention, there is also humoral control of myocyte hypertrophy, including endothelin, angiotensin II, and norepinephrine.

In patients with heart failure, a neurohormonal compensatory mechanism (i.e., the sympathetic nervous system and RAAS) is activated in an effort to maintain normal circulation.

SYMPATHETIC NERVOUS SYSTEM

Sympathetic activity is increased in patients with heart failure and bears a direct relationship to both disease severity and prognosis [21]. The sympathetic nervous system is responsible for maintaining circulatory stability in the face of decreased cardiac output. High levels of circulating norepinephrine can cause peripheral vasoconstriction. This may induce a reflex increase in vagal tone, which is a parasympathetic response. This in turn can reduce the heart's ability to respond to sympathetic stimulation. These effects may contribute to the decreased exercise tolerance experienced by patients with heart failure. Urinary excretion of catecholamines and circulating plasma levels of norepinephrine are elevated. Although sympathetic activity may support cardiovascular function in the short-term, long-term activation may exert adverse effects on the myocardium due to both the increased load caused by vasoconstriction and direct biologic action of norepinephrine on the myocardium [21].

Thus, consequences of decreased cardiac output and increased filling pressures lead to changes that are initially compensatory and help to restore cardiovascular homeostasis. However, shortly afterward, they are maladaptive and result in progressive neurohormonal activation and left ventricular remodeling. Systolic and diastolic heart failure result in a decrease in stroke volume. This leads to activation of peripheral and central baro- and chemo-reflexes that are capable of eliciting a marked increase in sympathetic nerve traffic. The ensuing elevation in plasma norepinephrine directly correlates with the degree of cardiac dysfunction and has significant prognostic implications. From a hemodynamic standpoint, increased vasoconstriction mediated by norepinephrine, angiotensin II, endothelin, vasopressin, and increased cardiac inotropy and chronotropy alters renal salt and water handling and enhances venous tone to facilitate end organ perfusion. The marked increase in cardiac and renal adrenergic activity reaffirms the fact that both the RAAS and the sympathetic system are co-activated and co-regulated.

BRAIN NATRIURETIC PEPTIDES

Brain natriuretic peptide, also known as B-type natriuretic peptide or BNP, was initially isolated from porcine brain in 1988 [22]. Despite its name, it is produced predominantly by the ventricular myocyte [23]. More accurately, N-terminal pro B-type natriuretic peptide (NT-proBNP) is the cardiac prohormone that is released from the ventricles in response to left ventricular volume expansion and pressure overload (i.e., to regulate blood pressure and fluid balance), and enzymes quickly convert NT-proBNP into the neurohormone BNP [24; 25]. NT-proBNP and BNP levels are known to be elevated in patients with left ventricular dysfunction and to correlate with echocardiographic findings, NYHA classification, and severity of heart failure [26]. The use of NT-proBNP and BNP as biomarkers in human heart failure continues to emerge, particularly as reference values, diagnostic sensitivities, specificities, positive predictive values, and cut-points become better defined for each [10]. For the purposes of this course, both biomarkers used in clinical practice will be referred to as BNP.

Atrial natriuretic peptide (ANP) and BNP are activated in response to atrial and ventricular volume/pressure expansion. They are released from the atria and ventricles to promote vasodilatation and natriuresis. Their hemodynamic effects are mediated by decreases in ventricular filling pressures, owing to reductions in cardiac preload and afterload. BNP, in particular, produces selective afferent arteriolar vasodilatation and inhibits sodium reabsorption in the proximal convoluted tubule [27].

BNP is a potent natriuretic, diuretic, and vasorelaxant peptide. It coordinates fluid and electrolyte homeostasis through its activity in the central nervous system and peripheral tissue. BNP promotes vascular relaxation and lowers angiotensin II, aldosterone, and endothelin-1. Its renal effects include increasing glomerular filtration rate and enhancing sodium excretion. Unlike ANP, whose major storage sites include the atria and ventricles, the major source of plasma BNP is cardiac ventricles. This suggests that BNP may be a more sensitive and specific indicator of ventricular disorders than other natriuretic peptides. The stimulus for BNP release is a change in left-ventricular wall stretch and volume overload, suggesting that BNP may be a "distress hormone," more specific for ventricular disorders than are other members of the natriuretic peptide family [28]. BNP is an independent predictor of high left ventricular end-diastolic pressure and is more useful than ANP or norepinephrine for assessing the mortality in patients with chronic heart failure [29]. Plasma levels can be used in diagnosis and prognosis of patients with heart failure, hypertension, myocardial infarction, right ventricular dysfunction, and cor pulmonale [30].

> **EB**
> EVIDENCE-BASED PRACTICE RECOMMENDATION
>
> According to the American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA), measurement of BNP or NT-proBNP is useful for risk stratification in chronic heart failure.
>
> (https://www.ahajournals.org/doi/10.1161/CIR.0000000000001063. Last accessed November 21, 2022.)
>
> **Strength of Recommendation/Level of Evidence**: 1A (Strong recommendation based on high-quality evidence from multiple randomized trials or meta-analyses)

The National Institutes of Health-sponsored Studies of Left Ventricular Dysfunction (SOLVD) in patients with chronic left ventricular dysfunction, but without signs of severe heart failure, demonstrated humoral activation that was characterized by increases in circulating ANP without activation of the circulating RAAS in the absence of diuretic treatment. Based upon the known biology of the natriuretic peptide system, it may play a key role in preserving the compensated state of symptomatic left ventricular dysfunction. Severe heart failure, unlike asymptomatic left ventricular dysfunction, is a syndrome characterized by sodium retention, action of RAAS, and elevation of both circulating ANP and BNP. Human and animal models of chronic severe heart failure are characterized by an attenuated natriuretic response to endogenous and exogenous natriuretic peptides. It has been suggested that the diminished renal response to cardiac natriuretic peptides plays an important role in the pathophysiology of sodium retention and systemic and renal vasoconstriction observed in severe heart failure, thus contributing to disease progression [31].

A key role for angiotensin II in mediating renal hyporesponsiveness to the natriuretic peptide system appears to be fundamental to severe heart failure. The natriuretic peptides and angiotensin II have renal actions at the same vascular and tubular sites within the kidneys. Angiotensin II may oppose the renal effects of the natriuretic peptides at both the glomerulus and the renal tubule, preventing the full natriuretic activity of this peptide. This in turn contributes to the sodium retention and edema formation of severe heart failure.

BNP biomarkers have demonstrated clinical utility for heart failure management [10]. However, there is limited information available to support the screening of broad populations to detect undiagnosed heart failure and/or symptomatic left ventricular dysfunction. A 2004 study suggests that elevated levels of BNP can be used as a cost-effective strategy for screening asymptomatic men and women older than 60 years of age with an ejection fraction <40% [32]. Although screening general populations with BNP is not recommended at this time, the results of a large randomized single-center study found that, among patients at risk of heart failure, BNP-based screening combined with collaborative care reduced the combined rates of left ventricular systolic dysfunction, diastolic dysfunction, and heart failure [33]. Further studies are needed to determine the cost-effectiveness and risk of such screening, as well as its impact on quality of life and mortality rate. Patients who are at very high risk of developing cardiomyopathy (e.g., those with a strong family history of cardiomyopathy) are appropriate targets for more aggressive screening, such as 2-D echocardiography, to assess left ventricular function.

ROLE OF VASOACTIVE SYSTEMS IN HEART FAILURE

Several studies have shown that heart failure is associated with increased circulating levels of proinflammatory cytokines. Cytokines are low-molecular weight proteins that are released by most cell types. Unlike hormones, cytokines are not stored but are secreted in response to specific stimuli. Cytokines are known to have significant interactions with neurohormonal pathways in heart failure. Insulin resistance is a recognized finding in patients with heart failure and has been suggested to be of prognostic value. The cytokines considered most relevant to the pathogenesis of heart failure are tumor necrosis factor and interleukin-6 [10]. The endothelin system and vasopressin also play a role in the pathogenesis of heart failure.

Interleukin-6 is a proinflammatory cytokine that has been implicated in the pathogenesis of heart failure. Patients with heart failure have a raised circulating interleukin-6 level, which is associated with a poor NYHA functional class, increased length of hospital stay, and poor left ventricular function. Furthermore, interleukin-6 may be important in the development of osteoporosis, which is known to occur in patients with heart failure [34].

Endothelin is a substance produced by the vascular endothelium that may contribute to the regulation of myocardial function, vascular tone, and peripheral resistance in heart failure. It binds to two receptors: ET-A, which exists in vascular smooth muscle and mediates vasoconstriction, and ET-B, which is found predominantly in endothelial cells and mediates vasodilatation through the release of nitric oxide. Endothelin-1 is a potent vasoconstrictor and has an exaggerated vasoconstrictive effect in the renal vasculature, reducing renal plasma blood flow, glomerular filtration rate, and sodium excretion [29].

Tumor necrosis factor has been implicated in response to various infectious or inflammatory conditions. Elevations in levels of tumor necrosis factor have been consistently observed in heart failure and seem to correlate with the degree of myocardial dysfunction. Tumor necrosis factor levels correlate positively with the degree of insulin resistance in heart failure and may be an important etiologic factor, as has been shown in the context of obesity-related insulin resistance [34]. Experimental studies also suggest that local production of this cytokine may have toxic effects on the myocardium. Genetic factors, including angiotensin-converting enzyme (ACE) gene and beta-adrenergic receptor polymorphisms, may influence the natural history of disease progression and response to treatment [29].

Vasopressin is increased in heart failure as a result of angiotensin II stimulation and the indirect effect of thirst. Under resting conditions, vasopressin is increased in heart failure compared with levels in normal subjects. However, the true physiologic importance of vasopressin is uncertain. Because angiotensin II is a major stimulus for vasopressin release, blockage of the renin-angiotensin-aldosterone system should attenuate the adverse effects of vasopressin. Partial substantiation for this is the reversibility of hyponatremia witnessed in response to the ACE inhibitors (ACEIs). However, hyponatremia is still common in heart failure, particularly in elderly patients who may otherwise be prone to this electrolyte abnormality. Potential clinical benefit exists in improved free water and electrolyte balance, reversal of peripheral and renal ischemia, and improved cognitive function. The role of vasopressin remains one of the underevaluated hormonal pathways in heart failure [35]. Initial studies with vasopressin receptor agonists (vaptans) have not shown long-term mortality benefit in patients with heart failure, despite improvements in body weight, urine output, serum sodium concentration, and cognitive functioning [36; 37; 38].

HYPOTHESIS FOR IMMUNE ACTIVATION

The main stimulus for the immune activation in heart failure is not known, but there are three main theories as to why this occurs. One hypothesis states that the heart is the main source of proinflammatory cytokines, as it has been shown that the failing myocardium is capable of producing tumor necrosis factor.

The second hypothesis is that bowel wall edema and ischemia that occur in heart failure due to venous congestion are responsible for bacterial translocation, leading to endotoxin release and subsequent immune activation. This hypothesis is further supported by the finding that patients have elevated concentrations of endotoxin and cytokines during an acute edematous exacerbation, which can be normalized by diuretic therapy. If the second hypothesis is true, it opens up the possibility for therapeutic strategies directed against the bacteria in the bowel wall, the endotoxin itself, or the binding of endotoxin to cells of the immune system.

The third proposed hypothesis is that the extramyocardial cytokine production due to tissue hypoxia may be the primary stimulus for increased tumor necrosis factor production in patients with heart failure. It may be the case that more than one mechanism is involved in causing the immune activation that occurs in heart failure [34].

DIAGNOSTIC ROLE OF CIRCULATING BNP

Based upon their elevation in chronic heart failure, circulating ANP and BNP have emerged as important diagnostic serum markers. With the known elevation of plasma BNP in heart failure, studies have focused upon its diagnostic usefulness. Elevated BNP has been found to be an excellent discriminator of cardiac and noncardiac dyspnea [31]. BNP was first used in the evaluation of dyspnea to measure the natriuretic hormones ANP and BNP in 52 patients presenting with acute dyspnea [39]. It was found that admission plasma BNP concentrations more accurately reflected the final diagnosis than ejection fraction or concentration of plasma ANP.

The rapid assay was first used in evaluating 250 patients presenting to the San Diego VA Health Care Urgent Care Center with dyspnea as their chief complaint [40]. Emergency department physicians blinded to the results of BNP measurements were asked to assess the probability of the patients having heart failure as the cause of his or her symptoms. Patients with the final diagnosis of heart failure (n=97) had a mean BNP concentration of 1076 ± 138 pg/mL while the non-heart failure group (n=139) had a mean BNP concentration of 38 ± 4 pg/mL. This distinction is perhaps the key element in the differential diagnosis of patients who present with acute dyspnea.

This study set the stage for the completed Breathing Not Properly Multinational study, a seven-center, prospective study of 1,586 patients who presented to the emergency department with acute dyspnea and had a BNP measured with a point-of-care assay upon arrival. Two independent cardiologists, blinded to BNP results, adjudicated the gold standard for heart failure. BNP levels alone were more accurate than any historical or physical findings or laboratory values in delineating the cause of dyspnea [28].

POINT-OF-CARE TESTING

Finding a simple blood test that would aid in the diagnosis and management of patients with heart failure would clearly have a favorable impact on the staggering costs associated with heart failure. The fact that a point-of-care assay for BNP has been approved by the U.S. Food and Drug Administration gives the clinician an opportunity to explore its potential usefulness. Serial point-of-care testing of BNP is of immense help in patients presenting to urgent care clinics. Patients who present to urgent care with dyspnea and BNP levels greater than 480 pg/mL have nearly 30-fold increased risk for a cardiac event in the next six months. BNP might also serve as a screen for patients referred for echocardiography. A low BNP level makes abnormal echocardiographic indices of left ventricular dysfunction (both systolic and diastolic) highly unlikely. In patients with clinical heart failure and normal ventricular function, a high BNP correlates

to diastolic filling patterns across the mitral valve and should probably be considered as part of the "criterion standard" for diagnosing diastolic dysfunction. BNP might also serve as a screening and early prevention tool for asymptomatic patients at high risk for heart disease, such as those with diabetes mellitus [10]. BNP might also be an effective way to improve the in-hospital management of patients admitted with decompensated heart failure [10; 29; 41; 42; 43].

The correlation between the drop in BNP level and the patient's improvement in symptoms suggests that BNP guided treatment might make "tailored therapy" more effective and may reduce the need for invasive hemodynamic monitoring in selected patients [5; 10].

BNP IN THE ACUTE CARE SETTING

Unfortunately, the signs and symptoms of heart failure are nonspecific, and a helpful history is often not obtainable in acutely ill patients. Dyspnea, a key symptom of heart failure, may also be a nonspecific finding in elderly or obese patients or those with a comorbidity of respiratory disease. Routine laboratory tests, echocardiography, and radiography are also not accurate enough to always make the appropriate diagnosis. It is difficult for clinicians to differentiate patients with heart failure from other diseases, such as pulmonary disease, on the basis of routinely available laboratory tests [29]. BNP measurements can be useful in establishing the cause of acute shortness of breath, but many patients have both pneumonia and heart failure, with high BNP levels and consolidation on the chest x-ray. Patients who present with chronic obstructive pulmonary disease exacerbation that has triggered worsening cor pulmonale may present with dyspnea and major signs of right ventricular volume overload, including massive edema and ascites. The same may be true in the setting of acute right ventricular failure caused by acute pulmonary embolism. In these patients, BNP levels are likely to be high (300–600 pg/mL), although not quite as high as in those with cardiac dyspnea from increased left ventricular end-diastolic pressure.

BNP levels correlate with outcomes in patients with heart failure. During treatment of decompensated heart failure, BNP levels generally decline, and lower BNP levels correlate with better outcomes [44]. A study conducted in 2009 demonstrated that patients with greater percent reduction in BNP or lower BNP levels after treatment of decompensated heart failure had better overall event-free survival, persisting beyond six months after the index episode [45]. Higher baseline levels did not normalize as often as lower levels, indicating that a uniform "target BNP" may not be feasible.

Finally, some patients may present with dyspnea as their clinical manifestation of acute myocardial infarction. BNP is also a marker of necrosis, and its level may be elevated in these patients. Some patients have presented to the emergency department with chest pain and shortness of breath as a manifestation of unstable angina, but no infarction. It is possible that increased BNP levels in these patients represent acute ischemia-induced left ventricular dysfunction and may, in fact, represent patients with large territories of myocardium at risk.

Echocardiography is the preferred method for the documentation of cardiac dysfunction at rest. It is the most important measurement of ventricular function of the left ventricular ejection fraction for distinguishing patients with cardiac systolic dysfunction from patients with preserved systolic function. It is generally considered the single most effective tool in widespread clinical use [46].

Correctly diagnosing heart failure, whether it is of new onset or decompensated, is only the first step, as appropriate triaging of the patient along with maximal treatment is extremely important in ensuring the well-being of the patients. The use of BNP levels might ultimately be helpful not only in assessing whether or not a dyspneic patient has heart failure, but also in making both triage and management decisions. In some emergency departments, the diagnosis of heart failure leads to immediate admission to the hospital. Admission levels of BNP are useful in establishing a prognosis in acutely decompensated heart failure, and predischarge levels can be useful to establish a postdischarge prognosis [10]. Yet, there are many patients who come in with only mild heart failure, often precipitated by dietary indiscretions or noncompliance with medications.

Because BNP is a volume-sensitive hormone with a short half-life (18 to 22 minutes), there may be a future for BNP levels in guiding diuretic and vasodilator therapy in patients presenting to the emergency department with decompensated heart failure. Research has shown that patients who were not readmitted in the 30 days after discharge could be characterized by decreasing BNP levels during hospitalization [28].

The UPSTEP (Use of PeptideS in Tailoring hEart failure Project) study evaluated the tailored treatment of heart failure according to BNP level. A substudy of UPSTEP assessed the change in percentage between BNP levels at the start of the study versus a specific week (i.e., 2, 6, 10, 16, 24, 36, or 48) [47]. Optimum cut-off percentage levels were obtained using a proportional regression analysis of death, hospitalization, and worsening heart failure. Patients with a decrease in BNP of more than 40% compared with that at study start and/or a BNP level less than 300 ng/L at week 16 had a significantly reduced risk of heart failure mortality and hospitalization [47]. Another study compared 18-month outcomes of BNP-guided versus symptom-guided heart failure therapy [48]. Both therapies resulted in similar rates of survival free of all-cause hospitalizations. BNP-guided therapy improved outcomes in patients 60 to 75 years of age but not in patients older than 75 years of age [48]. Knowing how fast BNP levels drop with treatment and what levels of BNP are needed to ensure patient stability might make it possible to use BNP-guided treatment algorithms for heart failure in the emergency department.

BNP IN THE OUTPATIENT SETTING

It seems that BNP levels may be helpful in guiding therapy in the outpatient setting. To make this a worthwhile endeavor, the following criteria should be met [29]:

- BNP levels should be measured accurately and rapidly. With the point-of-care assay for BNP, patients could have the BNP levels measured along with the electrolytes before coming to the outpatient clinic.

- Changing levels of BNP should represent either decompensation or improvement. Substantiating a diagnosis of decompensation might be one of the best uses of BNP in the outpatient setting. BNP levels should be useful in titrating therapy. However, this area is not yet clear. Delineating the magnitude of fluctuations of BNP levels in an individual patient over time should be ascertained before BNP levels can be used to titrate drug therapy.

There are many factors other than heart failure that can alter BNP values and circumstances in which BNP levels may be normal or lower than expected despite the presence of heart failure. Factors other than heart failure that can account for high BNP levels include [28]:

- Advanced age
- Renal failure
- Myocardial infarction
- Acute coronary syndrome
- Lung disease with right-side failure
- Acute, large pulmonary embolism
- High-output states, such as cirrhosis

Factors that may account for lower-than-expected BNP levels in the presence of heart failure include [28]:

- Flash pulmonary edema
- Stable NYHA Class I patients with low ejection fractions
- Heart failure secondary to causes upstream from the left ventricle
  - Acute mitral regurgitation
  - Mitral stenosis
  - Atrial myxoma

BNP levels are also elevated early in the course of an acute myocardial infarction. A second peak of BNP measured two to four days after a myocardial infarction is associated with remodeling of the heart and is a strong predictor of subsequent left ventricular dysfunction and mortality.

Some physicians prefer to use NT-proBNP levels to diagnose or monitor patients with heart failure. The Cleveland Clinic uses the following reference ranges for NT-proBNP [49]:

- Normal:
  - Less than 125 pg/mL for patients 74 years of age or younger
  - Less than 450 pg/mL for patients 75 to 99 years of age

- Indicates unstable heart function in patients with heart failure:
  - Greater than 450 pg/mL for patients younger than 50 years of age
  - Greater than 900 pg/mL for patients 50 years of age and older

The 2022 ACCF/AHA guideline recommends measurement of BNP or NT-proBNP for diagnosis (or exclusion), determining severity, and prognosis of heart failure or ADHF [10]. These biomarkers are useful for guiding medication dosing in certain patients with heart failure, but their usefulness for guiding therapy in ADHF is not established.

MANAGEMENT OF PATIENTS WITH SYMPTOMATIC AND ASYMPTOMATIC HEART FAILURE

The main goals of the treatment of heart failure are to reduce symptoms, prolong survival, improve the quality of life, and prevent disease progression. For patients who have developed left ventricular systolic dysfunction but who remain asymptomatic (Class I), the goal should be to slow disease progression by blocking neurohormonal systems that lead to cardiac remodeling. For patients who have developed symptoms (Class II–IV), the primary goal should be to alleviate fluid retention, lessen disability, and reduce the risk of further disease progression and death.

HISTORIC PERSPECTIVE OF HEART FAILURE THERAPY

Heart failure therapy and research can be viewed from a historical perspective using the "Eras of Heart Therapy," described by William T. Abraham, MD, former Chief, Division of Cardiovascular Medicine at the University of Kentucky [50].

Prior to 1980, during the nonpharmacologic era, treatments focused on lifestyle changes or limitations, such as bed rest, inactivity, and fluid restrictions. Hemodynamic agents, digitalis, and diuretics comprised the mainstay of treatment.

The 1980s marked the beginning of the pharmacologic era, which was heralded by the first Vasodilator Heart Failure Trial (V-Heft). During this time, digitalis and diuretics continued to be mainstays, but vasodilators — particularly the combination of nitrates and hydralazine — played a prominent role. The use of positive inotropes became prevalent.

The pharmacologic era continued into the 1990s, but the decade brought neurohormonal interventions to the forefront. ACEIs, beta-blockers, and spironolactone (for the treatment of advanced heart failure) were shown to alter the natural history of disease progression.

In the wake of disappointing results from drug trials, there has been an increased interest in devices for patients with heart failure. There have been important successes in randomized, controlled trials of cardiac resynchronization devices, implantable cardiac defibrillators, and ventricular assist devices (VADs). The successes of these devices and others to come are likely to have a major impact on clinical practice outcomes for patients with heart failure.

If pharmacologically halting the progression of myocardial pathology or countering the electrophysiologic mechanisms responsible for arrhythmias were possible, one would have no use for implantable defibrillators. In a significant percentage of patients who do not respond adequately to medical therapy, however, prevention or reversal of ventricular remodeling may be achievable with devices that synchronize ventricular contraction, reduce ventricular load, or directly impede ventricular dilatation [51].

MANAGEMENT OF FLUID STATUS

Diuretics

Many of the clinical manifestations of heart failure result from excessive salt and water retention, leading to inappropriate volume expansion of the intravascular compartment. Although both digitalis and low-dose ACEIs enhance urinary sodium excretion, few volume-overloaded patients with heart failure can maintain proper sodium balance without the use of diuretics. In short-term clinical trials, diuretic therapy has led to a reduction in jugular venous pressure, pulmonary congestion, peripheral edema, and body weight, all of which were observed within days of initiation of therapy. In intermediate-term studies, diuretics have been shown to improve cardiac function, symptoms, and exercise tolerance in patients with heart failure. To date, there have been no long-term studies of diuretic therapy in heart failure. Thus, their effect on morbidity and mortality are not clearly known. Although retrospective analyses of clinical trials suggest that diuretic use is associated with worse clinical outcomes, at least one

meta-analysis indicated that treatment with diuretic therapy produced a significant reduction in mortality and slowed the progression of heart failure [52].

A number of classification schemes have been proposed for diuretics on the basis of their mechanism of action, their anatomical locus of action within the nephron, and the form of diuresis that they elicit (i.e., solute versus water diuresis). The most common classification for diuretics is based on either the chemical (e.g., thiazide diuretic), site of action (e.g., loop diuretics), or clinical outcomes (e.g., potassium-sparing diuretics). Loop diuretics increase sodium excretion by up to 20% to 25% of the filtered load of sodium, enhance free water clearance, and maintain their efficacy unless renal function is severely impaired. In contrast, the thiazide diuretics increase the fractional excretion of sodium to only 5% to 10% of the filtered load, decrease free water clearance, and lose their effectiveness in patients with impaired renal function. Consequently, loop diuretics such as furosemide (most commonly used), bumetanide, and torsemide have emerged as the preferred diuretic agents for use in most patients [10; 46]. Diuretics should always be administered in the lowest dose possible and in combination with other guideline-directed medical therapy for heart failure that reduces hospitalizations and prolongs survival [10; 46].

Mineralocorticoid Receptor Antagonists

Mineralocorticoids, such as aldosterone, cause retention of salt and water and increase the excretion of potassium and hydrogen by binding to specific mineralocorticoid receptors. One mineralocorticoid, spironolactone, has antiandrogenic and progesterone-like effects, which may cause gynecomastia or impotence in men and menstrual irregularities in women. To overcome these side effects, eplerenone was developed. This drug has less sex hormone side effects than spironolactone. Although spironolactone and eplerenone are both weak diuretics, clinical trials have shown both of these agents to have pro-found positive effects on cardiovascular morbidity and mortality [10]. Patients using potassium-sparing diuretics should be monitored by repeated measurements of serum creatinine and potassium according to clinical status [10]. A practical approach is to measure serum creatinine and potassium every five to seven days after initiation of treatment until the values are stable. Thereafter, measurements can be made every three to six months [46; 53].

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

There is overwhelming evidence that ACEIs should be used in symptomatic and asymptomatic patients with a reduced ejection fraction <40% (HFrEF). ACEIs stabilize cardiac remodeling, improve patient symptoms, prevent hospitalization, and prolong life [10]. Data from the SOLVD Prevention Study, Survival and Ventricular Enlargement (SAVE) study, and the Trandolapril Cardiac Evaluation (TRACE) have shown that asymptomatic patients with left ventricular dysfunction who receive an ACEI will have less development of symptomatic heart failure and hospitalization. Asymptomatic patients with documented left ventricular systolic dysfunction benefit from long-term ACEI therapy. ACEIs markedly enhance survival in patients with signs and symptoms of heart failure after myocardial infarction [10].

ACEIs should be given as the initial therapy in the absence of fluid retention. In patients with fluid retention, ACEIs should be given together with diuretics. The dose of ACEIs should always be initiated at the lower dose level and titrated to the target dose. Changes in systolic and diastolic blood pressure and increases in serum creatinine are usually small in normotensive patients [10]. Regular monitoring of renal function is recommended before administration, one to two weeks after each dose increase, and at three- to six-month intervals [46; 53].

BETA-ANDRENERGIC RECEPTOR BLOCKERS

Beta-blocker therapy represents a major advance in the treatment of patients with heart failure with depressed ejection fraction [10]. When given in concert with ACEIs, beta-blockers reverse the process of left ventricular remodeling, improve patient symptoms, prevent hospitalization, and prolong life. There are three beta-blockers that have been shown to be effective in reducing the risk of death in patients with chronic heart failure: bisoprolol and sustained-release metoprolol succinate, which competitively block the ß1 receptor, and carvedilol, which competitively blocks the ß1, ß2, and ßa receptors. Use of one of these three beta-blockers is recommended to reduce mortality and hospitalizations in patients with HFrEF, with current or previous symptoms [10]. The favorable findings with these three agents should not be considered a beta-blocker class effect; other beta-blockers are not included in the recommendation for treatment of patients with heart failure [10].

Of the three beta-blockers that are approved for the treatment of heart failure, carvedilol has been studied most extensively. The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study extended these benefits to patients with more advanced heart failure. When compared with placebo, carvedilol reduced the mortality risk at 12 months by 38% and the relative risk of death or heart failure hospitalization by 31% [10]. In the Carvedilol or Metoprolol European Trial (COMET), carvedilol (25 mg twice daily) was compared with immediate-release metoprolol tartrate (5 mg twice daily) with respect to the primary end point of all-cause mortality. In this study, carvedilol was associated with a 33% reduction in all-cause mortality when compared with metoprolol tartrate. Based on the results of the COMET trial, short-acting metoprolol tartrate is not recommended for use in the treatment of heart failure.

The Compliance and Quality of Life Study Comparing Once-Daily Controlled-Release Carvedilol IR in Patients with Heart Failure (CASPER) was designed to test the hypothesis that the use of controlled-release carvedilol, a once-daily bioequivalent formulation of immediate-release carvedilol, could lead to improved drug-taking compliance. Simplifying a patient's regimen by reducing the frequency of medicine administration has the potential to improve compliance and may have a potentially favorable effect on physiologic measures (e.g., BNP), quality of life, and hospital utilization, as a significant proportion of hospital admissions for decompensated heart failure appear to be related to medication noncompliance. The results of this trial strongly support the safety of a simple and immediate switch from the twice-daily regimen of carvedilol to the once-daily controlled-release formulation. There was no excess of adverse events or safety issues identified [54].

ANTICOAGULATION AND ANTIPLATELET THERAPY

Patients with heart failure have an increased risk for arterial or venous thromboembolic events. In clinical heart failure trials, the rate of stroke ranges from 1.2% to 2.4% per year. Depressed left ventricular function is believed to promote relative stasis of blood in the dilated cardiac chambers with increased risk of thrombus formation. Treatment with warfarin is recommended for all patients with heart failure, chronic or paroxysmal atrial fibrillation, and a history of systemic pulmonary emboli, including stroke or transient ischemic attack.

Patients with symptomatic or asymptomatic ischemic cardiomyopathy and documented recent large anterior myocardial infarction or recent myocardial infarction with documented left ventricular thrombus should be treated with warfarin for the initial three months after a myocardial infarction, unless there are contraindications. There is no compelling evidence that warfarin anticoagulation is beneficial in patients with heart failure, although it may be considered in selected patients with heart failure after a careful assessment of the potential risks and benefits [10]. Aspirin therapy is recommended in patients with heart failure and ischemic heart disease for the prevention of myocardial infarction and death. However, lower doses of aspirin (81 mg) may be preferable due to the concern of worsening of heart failure at higher doses.

DIGITOXIN

A study performed on female rats suggested that digitalis glycosides may prolong survival in certain circumstances [55]. The study indicated two possible scenarios in which digitalis glycosides may provide a benefit: in the early onset of digitalis treatment after myocardial injury and in the treatment of patients with more accentuated ventricle dysfunction. Another study performed on 72 rats found that long-term treatment with digitoxin attenuates congestive heart failure, mitigates myocardial remodeling, and preserves calcium-binding myocardial proteins [56].

STATINS

There has been marked interest in the use of statin therapy in established heart failure in the last decade. In one study, statin therapy was associated with a reduction in mortality in patients with heart failure who were prescribed the drug [57]. These effects remained after accounting for the propensity to be treated with a statin upon hospital discharge. In addition to a reduction in overall mortality with statins, there was a 15% reduction in combined mortality and cardiovascular morbidity. The research-ers concluded that statin therapy was associated with significantly improved five-year mortality and morbidity in patients with heart failure who were discharged from the hospital [57]. A meta-analysis of primary- and secondary-prevention trials found that statins modestly reduced the risk of nonfatal heart failure hospitalization and a composite of nonfatal heart failure hospitalization and death, with no difference in risk reduction between patients who did or did not suffer myocardial infarction [58]. Statins are recommended to prevent symptomatic heart failure and adverse cardiovascular events in patients with a recent or remote history of myocardial infarction or acute coronary syndrome [10].

HISTORICAL ROLE OF NESIRITIDE IN THE TREATMENT OF ADHF

Nesiritide is the generic name assigned to recombinant human BNP. The physiologic effects of BNP are very similar to those of ANP. Both peptides result in increased venous capacitance, decreased vascular tone due to decreased sympathetic stimulation, and inhibition of the RAAS. The intravenous administration of nesiritide has been shown to produce favorable hemodynamic effects, including balanced vasodilatation associated with a rapid improvement in heart failure clinical symptoms. It also reduces levels of deleterious neurohormones, such as norepinephrine, aldosterone, and endothelin-1 [59].

Nesiritide emerged in 2000 in the Nesiritide Study Group trial, which enrolled patients hospitalized due to heart failure in either an efficacy trial or a comparative trial. The efficacy trial included 127 patients randomly assigned to double-blind treatment with placebo or nesiritide. The comparative trial included 305 patients randomly assigned to open-label therapy with standard agents or nesiritide for up to seven days. Nesiritide was found to improve both hemodynamic function and clinical status in both groups [60]. Nesiritide was subsequently approved by the FDA in 2001 [59].

In 2002, results of the Vasodilation in the Management of Acute Congestive Heart Failure (VMAC) trial were published [61]. VMAC evaluated the hemodynamic and clinical effects of nesiritide in addition to standard care compared with standard care plus IV nitroglycerin or placebo in 489 patients with acute decompensated heart failure and dyspnea at rest. This trial demonstrated that a 2 mcg/kg intravenous bolus given over one minute followed by a fixed infusion of 0.01 mcg/kg/min, rapidly, efficiently, and safely reduced pulmonary capillary wedge pressure while improving self-reported dyspnea index scales in patients with and without pulmonary artery catheters to monitor their central hemodynamics. In this trial, nesiritide was added to standard therapy (including dobutamine, dopamine, and parenteral diuretics) in patients hospitalized with acutely decompensated heart failure due to a wide variety of causes. Results indicated that nesiritide achieved greater hemodynamic and clinical benefits compared with intravenous nitroglycerin, with fewer adverse effects [30].

In 2005, two meta-analyses were published that raised questions about the safety and efficacy of nesiritide. In the first analysis, nesiritide use in 862 patients hospitalized for acute decompensated heart failure was associated with a 74% increased risk of 30-day mortality [62]. In the second, nesiritide use in 862 patients hospitalized for acute decompensated heart failure was associated with a 54% increased risk of worsening renal function [63]. A few months following publication of these analyses, the ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure included nesiritide in the section on interventions under active investigation [64]. The 2009 update to the guideline moved nesiritide from an active investigation status to a drug recommended for hospitalized patients comparative to nitroglycerin and nitroprusside [65]. The ASCEND-HF (Acute Study of Clini-

cal Effectiveness of Nesiritide in Decompensated Heart Failure) study, published in 2011, found no impact of nesiritide on either death or heart failure hospitalization [66]. However, the agent was found to have little benefit over existing therapies for the treatment of acute decompensated heart failure [67; 68; 69]. In 2018, the FDA reported that Janssen Pharmaceuticals was discontinuing manufacture of nesiritide, and the drug is no longer available in the United States [59].

IVABRADINE

In 2015, the novel cardiovascular agent ivabradine (a sinoatrial node modulator) was approved in the United States for the management of stable heart failure [70]. Ivabradine acts by inhibiting the hyperpolarization-activated cyclic nucleotide-gated channels within the SA node. The drug is indicated for patients who have symptoms of heart failure that are stable, who have a normal heartbeat with a resting heart rate of at least 70 beats per minute, and who are also taking beta-blockers at the highest dose they can tolerate [10; 70]. Possible side effects include atrial fibrillation, bradycardia, phosphenes, and hypertension [59; 70].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The ACC/AHA/HFSA asserts that ivabradine can be beneficial to reduce heart failure hospitalization and cardiovascular death for patients with symptomatic (NYHA class II–III) stable chronic heart failure (LVEF ≤35%) who are receiving guideline-directed evaluation and management and who are in sinus rhythm with a resting heart rate of 70 bpm or greater.

(https://www.ahajournals.org/doi/10.1161/CIR.0000000000001063. Last accessed November 21, 2022.)

Level of Evidence: 2a (Moderate recommendation based on moderate-quality evidence from one or more randomized controlled trials)

SACUBITRIL/VALSARTAN

Also in 2015, the combination angiotensin receptor-neprilysin inhibitor (ARNI) sacubitril/valsartan was approved for the treatment of heart failure after having been found to reduce the rate of cardiovascular death and hospitalization related to heart failure in these patients [10; 71]. However, results of a study published in 2019 indicate that the agent did not result in a significantly lower rate of total hospitalizations or deaths from heart failure [72]. This study included 4,822 patients with NYHA Class II to IV heart failure and ejection fraction ≥45% randomly assigned to receive sacubitril (97 mg)/valsartan (103 mg) twice daily, or valsartan (160 mg) twice daily. The incidence of death from cardiovascular causes was 8.5% in the sacubitril/valsartan group and 8.9% in the valsartan group. There were 690 hospitalizations for heart failure in the sacubitril/valsartan group and 797 hospitalizations in the valsartan group [72].

A randomized controlled trial (Prospective Comparison of ARNi with ACEi to Determine Impact on Global Mortality and Morbidity in Heart Failure [PARADIGM-HF]) compared sacubitril/valsartan with the ACEI enalapril in symptomatic patients with HFrEF tolerating an adequate dose of either ACEI or ARB [73]. In previous trials, enalapril improved survival in such patients. In the PARADIGM-HF trial, sacubitril/valsartan significantly reduced the composite endpoint of cardiovascular death or heart failure hospitalization by 20% compared with enalapril. A similar benefit was observed for death and heart failure hospitalization and was consistent across prespecified subgroups [73]. Use of an ARNI is more frequently associated with symptomatic hypotension and a comparable incidence of angioedema when compared with enalapril [73]. The efficacy of ARNI in patients with left ventricular dysfunction and heart failure in the early post-myocardial infarction period remains uncertain [10].

Potential adverse effects include hypotension, renal insufficiency, and angioedema. Sacubitril/valsartan should not be given with any ACEI, as this increases the risk for angioedema. Sacubitril/valsartan is to be used in place of an ACEI or an ARB and in conjunction with other standard heart failure treatments (e.g., beta-blocker, aldosterone antagonist). Patients must be able to tolerate ACEI or ARB before starting on sacubitril/valsartan [74]. The drug is also contraindicated in pregnant women [59]. Use of an ARNI is recommended to reduce morbidity and mortality in patients with HFrEF and NYHA Class II–III symptoms [10].

SODIUM-GLUCOSE COTRANSPORTER 2 (SGLT2) INHIBITORS

Beginning in 2020, the FDA has approved several sodium-glucose cotransporter 2 (SGLT2) inhibitors for adults with heart failure with reduced ejection fraction to reduce the risk of cardiovascular death and hospitalization [75; 76]. These agents, including dapagliflozin, empagliflozin, and sotagliflozin, have proven efficacy in reducing the risk of death and/or hospitalization in these patients, even in those without diabetes [77; 78; 148]. The 2022 AHA/ACC/HFSA guideline for the management of heart failure recommends SGLT2I for treatment of patients with symptomatic chronic HFrEF to reduce heart failure hospitalization and cardiovascular mortality, irrespective of the presence of type 2 diabetes [10]. Several randomized controlled trials in patients with type 2 diabetes who either have established cardiovascular disease or who are at high risk for cardiovascular disease have shown that SGLT2I prevent heart failure hospitalizations compared with placebo. Two trials showed the benefit of SGLT2I (dapagliflozin and empagliflozin) versus placebo on outcomes. Compared with placebo, SGLT2I reduced cardiovascular death or heart failure hospitalization by approximately 25%. The benefit in reduction of heart failure hospitalization was greater (30%)

in both trials. Additionally, the benefits in both trials were seen irrespective of baseline diabetes status [10]. The benefit appears independent of the glucose-lowering effects. The proposed mechanisms include reductions in plasma volume, cardiac pre- and afterload, alterations in cardiac metabolism, and reduced arterial stiffness [79; 80].

One study compared the effects of SGLT2I with the effect of ARNI in heart failure with reduced ejection fraction [81]. Among the six randomized controlled trials included, SGLT2I were found to significantly reduce risk of cardiovascular death or hospitalization for heart failure by 27% and all-cause death by 16%. The reduction was similar in patients both with and without diabetes. Indirect treatment comparison showed that SGLT2I and ARNI had similar effects and that a combination of the two achieved a better prognosis compared with ARNI monotherapy [81]. Another study found that therapy with SGLT2I did not significantly lower the risk of cardiovascular death or heart failure hospitalization when compared with ARNI [82].

DEVICES FOR THE TREATMENT OF HEART FAILURE

Primarily a disease of the elderly, heart failure continues to be an ever-increasing healthcare problem given the growth in the number of individuals older than 65 years of age. Although there have been many advances in the pharmacologic management of heart failure, there continues to be a significant number of patients with persistent symptoms despite maximal therapy, and it is likely that this group of patients will continue to increase in number.

Guidelines recommend the use of ACEIs, beta-blockers, diuretics, aldosterone antagonists, and digoxin for the treatment of patients with heart failure at various stages of the disease [83]. Despite advances in the pharmacologic management of heart failure, there remains a significant number of patients with persistent symptoms while on maximal medical therapy. Device therapies, such as ventricular synchronization, represent a promising modality in the treatment of patients with heart failure [84; 85].

The myocardial conduction system is vulnerable to the same pathophysiologic processes that occur in myocytes and interstitium, with altered conduction properties observed in response to ischemia, inflammation, fibrosis, and aging. Supraventricular arrhythmias, particularly atrial fibrillation, are often the precipitating events that herald the onset of either systolic or diastolic heart failure. Elevated ventricular end-diastolic pressure in a patient with hypertension or abnormal myocardial function leads to atrial stretch, which in turn incites electrical instability. Recognition of the presence of atrial fibrillation in a patient is critical, as several studies have demonstrated the effectiveness of oral anticoagulant therapy for the prevention of stroke.

Abnormal myocardial conduction can also lead to delays in ventricular conduction and bundle-branch block. Left bundle-branch block is a significant predictor of sudden death and a common finding in patients with myocardial failure. Its presence also affects the mechanical events of the cardiac cycle by causing abnormal ventricular activation and contraction, ventricular dyssynchrony, delayed opening and closure of the mitral and aortic valves, and abnormal diastolic function. Hemodynamics reveal a reduced ejection fraction, decreased cardiac output and arterial pressure, paradoxical septal motion, increased left ventricular volume, and mitral regurgitation. Ventricular arrhythmias are thought to be secondary to dispersion of normal conduction through nonhomogenous myocardial tissue, which promotes repetitive ventricular arrhythmias.

The rate of sudden cardiac death among persons with heart failure is six to nine times that seen in the general population. Major innovations in medical and device-based therapy for the primary and secondary prevention of lethal ventricular arrhythmias have occurred in the past decades. Increasing use of implantable cardioverter-defibrillators (ICDs) has reduced mortality in a subgroup of patients with heart failure [12].

The presence of dysrhythmias and conduction system abnormalities is an important characteristic of heart failure. Up to 53% of patients with heart failure have an intraventricular delay that can lead to abnormal electrical depolarization and subsequent dyssynchrony between the right and left ventricle. While many efforts have focused on optimization of preload, afterload, and contractility, technologic breakthroughs have made addressing the correction of ventricular dyssynchrony a possibility [84]. Ventricular desynchronization can lead to abnormal interventricular septal wall motion, reduction in stroke volume, reduction in the rate of rise of left ventricular pressure, diminished diastolic filling times, and prolongation of mitral regurgitation. Because all of these can contribute to worsening heart failure and symptomatic deterioration, the ability to correct this dyssynchrony is a very significant step in the treatment of heart failure.

To identify patients in whom ventricular dyssynchrony may be a problem, the presence of a bundle-branch block or intraventricular conduction delay on a standard electrocardiogram has been used, as these findings are the manifestation of ventricular dyssynchrony. In fact, the presence of a wide QRS complex has been shown to be an independent or contributing risk factor in patients with heart failure, with the degree of conduction delay possibly serving as a marker of disease severity.

Abnormal electrical signals that arise from damaged heart muscle may cause arrhythmias; therefore, arrhythmias are common in patients with heart failure. Remarkable advances in the technology and function of implanted cardiac devices have been achieved over the past 15 years. Most of these devices can be implanted with minor surgery that may be done as outpatient procedures or require only a day or two in the hospital. Leads are placed in the right upper and lower chambers of the heart.

A small computer is implanted under the skin, usually near the collarbone. These "built-in" computers have enormous potential to increase survival and the quality of life for the patients with heart failure. Patients with heart failure may be treated with permanent pacemakers, hemodynamic monitors, ICDs, or resynchronization devices. ICD therapy for primary prevention of sudden cardiac disease is recommended for select patients (i.e., expectation of meaningful survival greater than one year) to reduce total mortality and hospitalizations and improve symptoms and quality of life [10]. Periodic re-evaluation of ejection fraction following myocardial infarction, revascularization, or guideline-directed medical therapy is useful to determine candidacy for ICD or cardiac resynchronization therapy (CRT) [10]. Guideline-directed medical therapy should be optimized before ICD and CRT implantation to assess whether the left ventricular ejection fraction improves [10].

CRT is a pacemaker-based approach to the treatment of patients with heart failure who have a wide QRS complex on 12-lead electrocardiography. The purpose of resynchronization is to provide electro-mechanical coordination and improved ventricular synchrony in symptomatic patients who have severe systolic dysfunction and clinically significant intra-ventricular conduction defects, particularly left bundle-branch block [12].

Approximately 8% to 15% of patients with advanced heart failure have pacemakers implanted for symptomatic bradycardia, and an additional group of patients with heart failure have an implantable cardioverter defibrillator and use the bradycardia feature of the device to pace the right ventricle. Such patients have an increased risk of mortality or urgent transplantation due to progressive pump dysfunction. In one series, the risk at one year was 49% versus 15% in patients without a pacemaker. This difference may be due in part to the dyssynchronous contraction caused by right ventricular-based pacing. Whether such patients would benefit from the addition of a left ventricular lead is being studied.

One of the most important and overlooked aspects of resynchronization therapy is its potential to allow for maximal optimization of the pharmacologic treatment of heart failure. This can be achieved by the ability of the resynchronization device to help support blood pressure and heart rate while also treating arrhythmias [84].

When CRT is added to optimal medical therapy in patients in sinus rhythm, there is a significant decrease in patient mortality and hospitalization, a reversal of left ventricular remodeling, and improved quality of life and exercise capacity [86; 87; 88]. CRT reduces the interventricular mechanical delay and the left ventricular end-systolic volume index and increases the ventricular ejection fraction. Similar overall results with respect to the role of CRT were observed in the Comparison of Medical Therapy, Resynchronization, and Defibrillation Therapies in Heart Failure Trial (COMPANION) and in the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) trial [88; 89]. In the REVERSE trial and meta-analysis, CRT was shown to improve mortality in patients with and without ischemia, but patients with ischemia had less extensive reversal of left ventricular remodeling than those without ischemia [87; 88; 90].

The European Heart Rhythm Association/Heart Rhythm Society recommend cardiac resynchronization therapy rather than standard RV pacing for patients with symptomatic heart failure (HFmrEF) and an uncontrolled heart rate who are candidates for atrioventricular junction ablation (irrespective of QRS duration).

(https://academic.oup.com/eurheartj/article/42/35/3427/6358547. Last accessed November 21, 2022.)

Level of Evidence: IIa (Weight of evidence is in favor of usefulness/efficacy.)

Implantable Cardioverter Defibrillators

ICDs are pacemaker-like devices that continuously monitor the heart rhythm and deliver life-saving shocks if a dangerous heart rhythm is detected. They can significantly improve survival in certain groups of patients with heart failure who are at high risk of ventricular fibrillation. ICDs also have the ability to act as pacemakers for too-slow heart rates and can be modified to provide resynchronization therapy.

Patients with heart failure who may benefit from ICDs include those who have [91]:

- Survived a cardiac arrest
- A rapid, recurrent abnormal heartbeat such as sustained ventricular tachycardia
- A history of heart muscle damage caused by a prior heart attack. In clinical trials, ICDs were of particular benefit for individuals with cardiomyopathy caused by a prior heart attack.
- An ejection fraction of 30% or lower. A clinical trial of heart attack patients with low ejection fractions found that ICD therapy saved lives compared with those that had heart attacks alone.

Implantation of ICDs in combination with biventricular pacing is recommended to reduce the risk of sudden death and all-cause mortality in patients who remain symptomatic with severe heart failure NYHA Class II or III with left ventricular function ≤35% and QRS duration ≥150 ms, despite three or more months of treatment with optimal pharmacologic therapy, who are expected to survive for more than one year with good functional status [46]. It is considered reasonable in selected patients who have not experienced a myocardial infarction in the past 40 days and who are on optimal background therapy, including ACEIs, beta-blockers, and an aldosterone antagonist, to reduce sudden death [46]. ICD therapy is not indicated in patients in NYHA Class IV with severe, drug-refractory, symptoms who are not candidates for CRT, a ventricular assist device, or cardiac transplantation [46].

Primary prevention of death in patients with left ventricular dysfunction, prior infarct scar, and non-sustained ventricular tachycardia with an ICD versus antiarrhythmic drug therapy or no therapy has been investigated in the several large trials, including the Multicenter Automatic Defibrillator Implantation Trial (MADIT II) and the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial. These studies used either invasive electrophysiologic studies or signal-averaged electrocardiogram to identify high-risk patients eligible for randomization.

The MADIT II examined the use of ICDs in a broad population of heart patients enrolled with ischemic cardiomyopathy and an ejection fraction <35%. Results were highly significant and pointed to a 31% reduction in all-cause mortality. However, more research is needed on the use of ICDs for patients with more advanced heart failure, as less than one-third of the study participants had NYHA Class III/IV heart failure [46].

Outcomes and results of the MIRACLE trial have shown CRT in patients with NYHA Class III/IV heart failure provides a variety of beneficial effects, including improved quality of life, increased six-minute walk distance, improved NYHA functional class ranking, increased peak ventilatory oxygen, improved treadmill exercise time, reduced QRS duration, improved cardiac structure and function, and fewer hospitalizations over six months [10; 50].

Cardiac resynchronization not only increased the likelihood of clinical improvement, but also reduced the risk of clinical deterioration during the course of follow-up. Patients in the resynchronization group were less likely than those in the control group to require treatment with an intravenous medication for worsening heart failure. Furthermore, cardiac resynchronization was associated with fewer admissions to the hospital and with fewer days in the hospital for the treatment of heart failure. The combined risk of a major clinical event (death or hospitalization for heart failure) was 40% lower in the resynchronization group than the control group.

The findings of this study are consistent with the results of earlier studies that reported both hemodynamic and symptomatic improvement after cardiac resynchronization. The effects of resynchronization on the combined risk of death and worsening heart failure seen in the study are encouraging [92]. The Echo-CRT trial and a meta-analysis suggest possible harm from CRT when QRS duration is <130 ms. Implantation of CRT is not recommended in this case [46; 93; 94; 95].

Cardiac Resynchronization (Biventricular Pacemakers)

Heart failure accounts for more than 1 million hospitalizations every year in the United States [96]. One-half of the deaths among these patients are caused by progressive cardiac dysfunction, which pacemakers help correct by stimulating the heart muscle to contract, improving perfusion of the body [92].

Using specialized pacemakers to recharge the weakened hearts of select patients with heart failure can lower the death rate from the disease and reduce hospitalizations [92]. These specialized pacemakers have been known to improve the quality of life for select patients with heart failure [97].

According to clinical trial results with selected patients, CRT:

- Increases the amount of daily activities patients perform without experiencing symptoms of heart failure
- Extends the exercise capacity of patients with heart failure, as shown by the distance walked in six minutes
- Promotes changes in the anatomy of the heart that improve cardiac function
- Reduces the number of days patients spend in the hospital and the total number of hospitalizations
- Reduces heart failure deaths

In approximately 30% of patients with chronic heart failure, the disease process not only depresses cardiac contractility but also affects the conduction pathways by causing a delay in the onset of right or left ventricular systole. Such dyssynchrony is apparent on the electrocardiogram as a QRS interval lasting more than 120 ms [92].

One analysis comparing pacemaker therapy versus no therapy in patients with dysfunction of the left ventricle involved four studies of 1634 patients. The majority of patients were men with severe heart failure. The patients were divided into two groups: those who received cardiac resynchronization and those who did not. Cardiac resynchronization reduced death from progressive heart failure by 51% [92]. The death rate was 1.7% for those who received resynchronization and 3.5% for those who did not. The pacemaker therapy also reduced hospitalizations by 29% and showed a trend toward reducing death by any cause [92].

As noted, cardiac resynchronization (biventricular pacemaker) therapy involves transvenous placement of three leads (one atrial lead and two ventricular leads), which may be accomplished in an outpatient setting. Some patients may require a thorascopic or mini-thoracotomy procedure for left ventricle lead placement, which would require a brief inpatient hospital stay. The right atrial and ventricular leads are standard leads placed in the right heart chambers. The left ventricular lead is placed in a cardiac vein via the coronary sinus. Following verification of lead placement, lead stability, sensing, and pacing thresholds, the device is activated.

After implantation, the pacemaker device is programmed so that both ventricles are stimulated at the same time after atrial contraction. This improves left ventricular diastolic filling time, reduces presystolic mitral regurgitation, and improves left ventricular function. Because the optimization of timing and the atrioventricular delay are a function of cardiac resynchronization therapy, patients with long atrio-ventricular delay may be particularly well suited to this therapy. It has been estimated that 60% of patients with heart failure may be eligible for CRT but that it is underutilized by most U.S. hospitals [98; 99].

Based on echocardiographic data, results from the MIRACLE study, the Study of Vigor in Congestive Heart Failure (VIGOR-CHF), and the Multisite Stimulation in Cardiomyopathies (MUSTIC) trial suggest that biventricular pacemaker pacing is associated with reverse remodeling and a reduction in hospitalizations in patients with heart failure [97]. This was evidenced by the fact that biventricular pacing produced a very significant reduction in left ventricular mass, significant reductions in jet area, and a significant reduction in both left ventricular end-systolic and end-diastolic dimensions [84].

Biventricular pacing to achieve cardiac resynchronization is a promising therapy for patients with heart failure and an ICD. Initial results suggest that biventricular pacing can improve exercise tolerance and NYHA functional class in these patients. It has also been found to improve symptoms and reduce hospitalizations in patients with heart failure [50; 97]. Given the very debilitating symptoms patients with heart failure experience, often despite maximal medical therapy, the need for an adjunctive therapy such as resynchronization therapy is clear. However, the use of resynchronization devices is limited by the technical skill required to implant these devices, lack of organization in the system of cardiac care, and the need for longer term follow-up [97]. Based on the rapid pace of innovation and development in this field, these limitations are sure to be overcome [84].

The available evidence suggests that CRT can provide enhanced quality of life for selected patients with severe heart failure. Patients enrolled in the clinical trials consistently reported enhanced quality of life as measured by the Minnesota Living with Heart Failure scale [100].

Novel Devices

In 2019, the FDA approved the Barostim Neo System for patients with heart failure not suited for cardiac resynchronization therapy [101]. The device was given "breakthrough device" designation because it treats a life-threatening disease (i.e., heart disease) and addresses an unmet medical need [102]. The system includes an implantable pulse generator that connects to a lead attached to the carotid artery. It delivers electrical impulses to baroreceptors in the neck then relays information to the brain. The brain then sends signals to the heart and blood vessels that relax the blood vessels and inhibit the production of stress-related hormones to reduce heart failure symptoms. The FDA evaluated data from a multi-center randomized clinical trial of 408 patients with advanced heart failure. All patients received guideline-directed medical therapy and 125 patients also received the implant. Patients who received the implant showed improvements in six-minute walking distances and quality of life. Potential side effects include infection, reimplantation, dizziness, fainting, arterial damage, exacerbation of heart failure, stroke, and death [101].Also in 2019, the FDA approved the Optimizer Smart system as a breakthrough device for treatment of patients with chronic, moderate-to-severe heart failure who are not suited for treatment with other heart failure devices (e.g., CRT) [103]. The Optimizer Smart system is comprised of several components, including an implantable pulse generator, battery charger, programmer, and software. The pulse generator is implanted beneath the skin in the upper left or right area of the chest and connected to three leads that are implanted in the heart. After the device is implanted, a physician tests and programs the device, which delivers electrical impulses to the heart during regular heartbeats to help improve the heart's contraction capability [103]. The FDA evaluated data from two randomized, multi-center clinical trials with a total of 389 patients with moderate-to-severe heart failure. All patients received optimal medical therapy and 191 patients also received an Optimizer Smart system implant. Patients receiving the implant showed improvements in the distance they were able to walk in six-minute walking tests and on standard assessments to measure heart failure

symptoms (e.g., quality of life and functional status) compared with those who received only medical therapy. Potential complications include infection, bleeding, worsened heart failure, or problems with the device itself (e.g., dislodgement) [103].

HEART TRANSPLANTATION

Heart transplantation is an accepted treatment option for end-stage heart failure. Although controlled trials have never been conducted, it is considered to significantly increase survival, exercise capacity, return to work, and quality of life compared with conventional treatment. Patients who should be considered for heart transplantation are those with severe symptoms of heart failure with no alternative form of treatment and with a poor prognosis. Besides shortage of donor hearts, the main problem with heart transplantation is rejection of the allograft, which is responsible for a considerable percentage of deaths in the first postoperative year. The long-term outcome is limited predominantly by the consequences of immunosuppression [46].

LEFT VENTRICULAR ASSIST DEVICES

Although typically considered a bridge to transplant device, left ventricular assist devices (LVADs) are extending the life of patients with heart failure as permanent or destination therapy. Additionally, survival after transplant is similar or increased when bridging with a LVAD is used. LVADs can be a good option for patients not eligible for transplantation; 80% of these individuals survive to one year and 70% survive at least two years post-implantation with a continuous-flow LVAD. Patients up to 70 years of age without cardiogenic shock, diabetes, or renal impairment have a survival of 85% at two years with a continuous-flow LVAD. Bleeding, thromboembolism, pump thrombosis, driveline infections, and device failure are still significant problems affecting long-term patient outcomes, despite technologic advances [46; 104]. Additionally, an estimated 60% of patients are rehospitalized at least once by six months postimplantation [104]. Consensus-based contraindications to LVAD therapy include active malignancy or active infection; severe liver, lung, or vascular disease; significant aortic insufficiency; and inhibiting psychosocial factors [104].

REVASCULARIZATION AND SURGICAL THERAPY

Patients with heart failure of any stage who are at risk for coronary artery disease should be screened for myocardial ischemia [105]. Revascularization, through either a catheter-based or a surgical approach, often improves ischemic symptoms, improves cardiac performance, and reduces the risk of sudden death. In select patients with heart failure, reduced EF (≤35%), and suitable coronary anatomy, surgical revascularization plus guideline-directed medical therapy is beneficial to improve symptoms, cardiovascular hospitalizations, and long-term all-cause mortality [10]. Patients with Stage C or Stage D heart failure, who have been considered unacceptable candidates for surgery, may in fact derive substantial benefit from bypass surgery and additional techniques designed to reduce myocardial wall stress. Procedures to eliminate or exclude areas of infarction, repair mitral regurgitation, or support the failing myocardium are undergoing clinical trials [105]. Similarly, the role of mechanical devices that serve to support patients who are awaiting heart transplantation or are definitive therapy for end-stage (Stage D) heart failure continues to evolve, and such devices offer great hope to many patients who are not eligible for cardiac transplantation [12; 104].

Results are available from at least one trial, the Surgical Treatment for Ischemic Heart Failure (STICH) trial, which compared the addition of coronary artery bypass grafting (CABG) to medical therapy versus medical therapy alone. The most common types of death—sudden and pump failure—were significantly reduced with CABG (as were severe ischemic events), but these gains were offset by an increase in post-procedure deaths (i.e., surgical therapy did not statistically reduce the primary outcome of all-cause mortality) [106]. The greatest benefit of CABG was survival at the two-year mark, and the STICH Extension study is investigating the benefit beyond 24 months.

IMPEDANCE CARDIOGRAPHY

The management of heart failure has become increasingly difficult. One of the greatest challenges in managing chronic heart failure is obtaining objective data that signals disease progression or therapeutic effectiveness. It is believed that hemodynamic parameters, such as indices of cardiac output, contractility, fluid content of the chest, and ventricular workload, provide the needed information to augment medical decision making. However, in the past, it was neither feasible nor cost-effective to obtain serial hemodynamic measurements in outpatient settings. Heart failure professionals had to rely on clinical signs and symptoms of worsening heart failure as their primary source of data for clinical decision making in these settings. The development and evolution of impedance cardiography, also referred to as thoracic electrical bioimpedance, specially adapted for measuring cardiac stroke volume is a valid, accurate, and reproducible alternative for obtaining the needed hemodynamic data. Impedance cardiography utilizes changes in thoracic electrical impedance to estimate changes in blood volume in the aorta and changes in fluid volume in the thorax [107]. The device is a hemodynamic monitor that uses thoracic electrical bioimpedance (TEB). TEB is a method of measuring the impedance or resistance to the flow of electricity through the chest cavity. Because this resistance changes with respiration and pulsatile flow of blood through the chest, this technique can be used to measure respiratory and hemodynamic parameters.

The application of TEB technology in the assessment of cardiac function is known as impedance cardiography. Impedance cardiography was originally introduced in the late 1930s. However, systematic study of TEB technology was delayed until the late 1960s when the National Aeronautics and Space Administration (NASA) considered it for use in monitoring astronauts during the Apollo manned flight into space.

Despite significant advances in scientific knowledge and technology in the latter half of the 20th century, one of the greatest challenges in managing patient care is the need for readily accessible, objective data that signals disease progression and/or treatment effectiveness. Obtaining, recording, and trending this data is dependent upon technology that produces valid, reproducible, and cost-effective measurements of cardiac function in a timely manner. While both invasive and noninvasive technologies have been developed and used effectively in the assessment, diagnosis, and evaluation of treatment outcomes, most require specialized environments, costly equipment, and specially trained medical personnel to obtain and/or interpret the data. Because of the cost and/or risk associated with these technologies, repeated hemodynamic measures that would enhance medical management and fine tuning of care are not obtained in ambulatory care settings, which is the focus of care for a major portion of the population of patients with heart failure for a significant period of illness.

The contemporary focus of disease management is shifting from symptom management to evaluating hemodynamic performance, including cardiac output, left ventricular volumes, and ejection fraction. Objective, accurate, reproducible, and easy-to-obtain measurements of physiologic parameters that are indicators of hemodynamic function are essential for managing both predisposing conditions and heart failure itself. Heart failure represents one of the chronic disorders for which management might be improved with the use of impedance cardiography. This potential exists for three specific reasons. First, both recognizable hemodynamic abnormalities and the accumulation of thoracic fluid characterize worsening heart failure. Second, changes in hemodynamic variables and in thoracic fluid content are clinically relevant when assessing improvement or progression of the disease process and are regarded as appropriate targets for therapeutic intervention.

Third, physicians are generally unable to assess hemodynamic variables and thoracic fluid content, or changes in these variables, accurately using either clinical judgment or any commonly available noninvasive technique. Therefore, it is appropriate to hypothesize that impedance cardiography may be able to identify clinically relevant changes in hemodynamic variables or thoracic fluid content earlier or more accurately than the usual clinical assessment carried out by physicians. Therefore, it might be appropriate to recommend the routine use of impedance cardiography and to expect that it may enhance patient care and improve outcomes of patients with chronic heart failure as well as other chronic cardiopulmonary disorders. To further increase the knowledge of the importance of bioimpedance data in optimizing patient management, the following case studies will be presented.

Case One: Determining Whether Changes in the Medical Regimen Are Warranted

Patient A is man, 65 years of age, with dilated cardiomyopathy of seven years duration and a left ventricular ejection fraction of 12%. He presented to the heart failure clinic for a routine evaluation. The patient denied symptoms of heart failure over the preceding months. He was on a regimen of quinapril 20 mg twice a day, furosemide 80 mg daily, and digoxin 0.25 mg daily. The patient had been intolerant of beta-blockers in years past due to profound bradycardia. Physical examination was notable for a blood pressure of 120/90 mm Hg, increased jugular venous pressure, and an audible murmur. TEB revealed a cardiac index of 1.7, systemic vascular resistance (SVR) of 2,249, and a thoracic fluid content of 0.0035. On a previous periodic evaluation four months prior, the cardiac index (a measure of cardiac output) was 2.5 $L/min/m^2$, with an SVR of 1,400 and a thoracic fluid content of 0.0034. In spite of the patient's asymptomatic state, this change in his hemodynamics led to a recommendation to increase his quinapril to 40 mg twice daily.

Upon repeat evaluation four weeks later, Patient A's blood pressure was 108/72 mm Hg, and he had an otherwise negative cardiac examination. Repeat TEB showed a cardiac index of 2.4, with an SVR of 1,398 and a thoracic fluid content of 0.028. In view of the achievement of these target values, no changes were made in his medications on this visit.

On another periodic visit three months later, Patient A again stated that he felt well and denied dyspnea, orthopnea, or edema. His blood pressure was 102/80 mm Hg, and he had increased jugular venous pressure with a mild hepatojugular reflux. However, there were no other pulmonary and cardiac findings. Repeat hemodynamic indices revealed a cardiac index of 2.7, with an SVR of 1,123 and a thoracic fluid content of 0.041. This elevated thoracic fluid content prompted an increase in his diuretic therapy. Two years later, Patient A has remained asymptomatic on this stable medical regimen.

Case Two: Assessing Hemodynamic Correlates of a Change in Symptoms

Patient B, a woman 71 years of age with idiopathic dilated cardiomyopathy, an eight-year history of symptomatic heart failure, and an ejection fraction of 25% presented with complaints of fatigue, lethargy, and thirst on a regimen of lisinopril 20 mg daily, digoxin 0.125 mg daily, and bumetanide 2 mg daily. Examination showed a blood pressure of 84/60 mm Hg, pulse rate between 80 and 88 beats per minute (bpm) with atrial fibrillation, clear lungs, no gallop, and no pedal edema. Noninvasive hemodynamics showed a cardiac index of 2.5, with an SVR of 1,497 and a thoracic fluid content of 0.029. It was thought that Patient B's symptoms were likely related to volume depletion, and diuretics were temporarily discontinued. She was scheduled for a follow-up visit, with instructions to measure her weight daily.

Two weeks later, Patient B presented with complaints of abdominal fullness and a one-pound weight gain, without dyspnea or peripheral edema. Blood pressure was 100/80 mm Hg, pulse was 85 bpm, and prominent jugular venous distention was noted.

There was an audible mitral regurgitant murmur and moderate hepatomegaly with no peripheral edema. Hemodynamics showed a cardiac index of 1.6, with an SVR of 2,883 and a thoracic fluid content of 0.052. Despite the minimal weight gain, it was apparent that the patient was significantly volume overloaded, and bumetanide was resumed at its previous dose. She was also instructed to take metoprolol 25 mg daily after resumption of bumetanide.

After two weeks, a repeat evaluation revealed complaints of minimal dyspnea, a blood pressure of 90/60 mm Hg, a heart rate of 90 bpm, and a weight decrease of one pound from the previous visit. Neck veins were no longer distended. Per noninvasive readings, the cardiac index was 2.2, the SVR 2,710, and the thoracic fluid content was 0.026. Metoprolol was increased to 50 mg daily and subsequently to 100 mg daily.

Evaluation four weeks later showed a blood pressure of 96/60 mm Hg, a pulse rate of 80 bpm, and a weight decrease of one more pound. The cardiac index at this time was 2.7, with an SVR of 1,626 and a thoracic fluid content of 0.032. Patient B's symptoms, physical findings, and hemodynamic indices remained stable over the ensuing two years on this medical regimen.

Case Three: Measuring Hemodynamics on Periodic Follow-up Visits

Patient C, a man 80 years of age with ischemic dilated cardiomyopathy, was referred for optimal medical management because of continuing problems with fatigue despite therapy with furosemide 40 mg twice daily, losartan 50 mg twice daily, doxazosin 2 mg daily, and amiodarone. Physical examination revealed a blood pressure of 122/70 mm Hg, pulse of 60 bpm, flat neck veins, and mitral regurgitant murmur. There was no peripheral edema. Noninvasive hemodynamics showed a cardiac index of 4.0, with an SVR of 770 and a thoracic fluid content of 0.047. It was recommended that Patient C begin beta blockade, and in view of the low SVR, metoprolol (rather than carvedilol) was selected as the drug of choice, at an initial dose of 25 mg daily.

Two months later, Patient C returned complaining of lethargy on this new regimen. His blood pressure was 70/48 mm Hg, the pulse was 58 bpm with mitral regurgitant murmur. His cardiac index was 5.2, the SVR was 428, and the thoracic fluid content was 0.043. Furosemide was discontinued and losartan reduced to 50 mg daily.

On subsequent visits, Patient C's blood pressure rose to 110/78 mm Hg, his pulse was 52 bpm, and his remaining cardiac exam unchanged. The cardiac index was now 4.8, the SVR 751, and the thoracic fluid content was 0.047. On this regimen the patient felt remarkably better. Over the ensuing two years he remained clinically stable, on 100 mg of metoprolol daily, with unchanged hemodynamics [107].

Case Four: Tracking Trends in Hemodynamic Parameters After Alterations in Drug Therapy

Patient D, a man 79 years of age, presented to the outpatient clinic on continuous home dobutamine. After a 30-year history of progressive dilated cardiomyopathy, with ejection fraction of <15%, he was hospitalized for progressive heart failure despite aggressive outpatient medical management. Pulmonary artery catheterization revealed a cardiac index of 1.3, which increased to 2.0 while on dobutamine. Multiple attempts at discontinuation of the drug proved futile, and he was eventually discharged on an infusion of 5 mcg/kg/min of continuous dobutamine. After six weeks, he presented for an outpatient visit. In addition to dobutamine, he was on spironolactone 25 mg daily, lisinopril 10 mg daily, digoxin 0.25 mg daily, and furosemide 80 mg daily. He felt well, was able to walk one mile without dyspnea, and now denied any symptoms of heart failure. The blood pressure was 110/67 mm Hg, his pulse was about 85 bpm in chronic atrial fibrillation, and central venous pressure was normal. The remaining exam was notable only for a grade II/VI mitral regurgitant murmur. Noninvasive hemodynamics showed a cardiac index of 2.8, an SVR of 1,081, and thoracic fluid content of 0.023. In view of these excellent hemodynamics and the patient's asymptomatic status, dobutamine was discontinued in the office while undergoing continuous hemodynamic monitoring using TEB. Surprisingly, over the ensuing hours his hemodynamics remained unaltered despite discontinuation of the dobutamine infusion. Patient D was sent home off intravenous dobutamine and on escalating doses of metoprolol. Over the ensuing weeks, he remained clinically stable, and repeat thoracic bioimpedance hemodynamics showed a cardiac index of 2.9, an SVR of 932, and a thoracic fluid content of 0.027, despite the reinstitution of metoprolol and the discontinuation of dobutamine. Three months later, a periodic follow-up was done with Patient D on metoprolol 100 mg daily, lisinopril 20 mg daily, spironolactone 25 mg daily, digoxin 0.25 mg daily, and furosemide 80 mg daily. He complained of fatigue but was still able to walk one mile without dyspnea and denied having orthopnea or pedal edema. Physical examination revealed no evidence of volume overload but repeat hemodynamic showed a cardiac index of 1.8, an SVR of 1,752, and a thoracic fluid content of 0.018. In view of the increased SVR and reduced cardiac index, lisinopril was increased to 20 mg twice daily, and in hopes of achieving further sympathetic withdrawal, metoprolol was increased to 150 mg daily. The patient was stable on this clinical regimen and remained asymptomatic [107].

Results of the IMPEDANCE-HF trial support the concept that impedance-guided treatment reduces hospitalizations for acute heart failure as well as the incidence of heart failure and cardiovascular and all-cause mortality [108]. Results of another study found that impedance cardiography did not reliably track stroke volume or cardiac output changes during a rehabilitation program compared with echocardiography. The AHA/ACC/HFSA guideline states that further study of impedance cardiography is needed before it can be recommended for routine clinical care [10].

AN INTEGRATED APPROACH TO HEART FAILURE MANAGEMENT: HEART FAILURE CLINIC DISEASE MANAGEMENT PROGRAMS

DISEASE MANAGEMENT PROGRAMS

Despite compelling scientific evidence that pharmacologic therapy, such as ACEIs, beta-blockers, and aldosterone antagonists, reduces hospitalizations and mortality in patients with heart failure, these life-prolonging therapies continue to be underutilized outside the highly artificial environment of clinical trials. Indeed, numerous studies in a variety of different clinical settings indicate that a significant proportion of patients with heart failure are not receiving treatment with evidence-based, guideline-recommended therapies. Treatment gaps have also been documented in the provision of other components of care for patients with heart failure, especially in the critically important area of patient education [109; 110; 111]. Being unhoused, substance use, food insecurity, limited English proficiency, intimate partner violence, elder abuse, social isolation, and lack of transportation represent potential barriers to optimal disease management [10].

Numerous studies have shown that many of the challenges to delivering optimal care to patients with heart failure can be met through an integrated specialized heart failure clinic approach that utilizes nurse and physician extenders to deliver and ensure the implementation of care [112]. Although disease management strategies can lead to improved survival, it is not clear that these strategies are necessarily more cost effective [10]. Accordingly, the biggest challenge to disease management programs is to determine how to support the additional personnel required in this model of care.

SETTING UP A HEART FAILURE CLINIC

Any effort at the establishment of a heart failure clinic requires a methodical process that first seeks to examine the local operative conditions that influence therapeutic interventions. There are key questions which should be prospectively tackled. First, determine which process works best. Next, define the patient population that will be treated. The next step is to determine the most effective way to modify patient behavior, because this is the key to changing outcomes in patients with heart failure. To define the economic feasibility of setting up a heart failure clinic, one must know the cost of care for heart failure as well as the average length of stay in the hospital setting. Furthermore, the 30- and 90-day readmission rates should be calculated. Other important points to consider relate to the current approach to these patients in the local emergency room. Finally, knowing about the structure of payments and payer classes is important [113].

One should understand where the important financial responsibilities and opportunities lie in the global heart failure care process. Clearly, setting up an outpatient service is associated with a cost increase. This is a result of the additional resources that are developed, the cost of increased telephone management, the cost of the education component, and the cost of increased pharmaceutical use in the outpatient setting. On the other hand, the cost savings are most noticeable in the hospital and the emergency department. Should the hospital pay the increased costs to implement outpatient care processes? The obvious answer is yes. This type of financial alignment is very important in a move to a nontraditional heart failure care process [7].

The traditional format of healthcare delivery for the patient with heart failure has centered around crisis intervention, a concept that allows patients to reach a point in their illness that requires acute care followed by a cycle of prolonged and repeated hospitalizations. Thus, of the four areas where heart failure care is provided (outpatient, home, hospital, and emergency department), the hospital and the

emergency department have been the major areas of focus. The emerging paradigm for heart failure care now dictates that the traditional focus must shift to the outpatient and home settings, with an emphasis on preventative intervention designed to break away from the vicious cycle of repeated and prolonged hospitalizations. These concepts have led to the development of outpatient strategies, which have resulted in the creation of heart failure treatment centers [7; 114].

In an effort to provide better care, doctors and nurses have set up special disease management programs for patients with heart failure. Hospitalizations and emergency visits for heart failure have decreased, and functional status, peak oxygen consumption, and quality-of-life scores have improved [115]. The key elements present in these programs are [113]:

- A multidisciplinary team
- Practice guidelines
- Systems for following patients at home
- Data collection at regular intervals to measure outcomes
- Patient education and self-care maintenance

Perhaps one of the critical features of a successful heart failure clinic is a core of professionals who have excellent knowledge of the concepts and will work diligently to maintain the goal of enhanced quality of life for their patients. There is no specific number of people needed to initiate a successful clinic. However, commitment is crucial, and results are usually best when clinic development is part of a plan of care that includes support by administration, nurses, physicians, ancillary personnel, and even local insurers.

A MULTIDISCIPLINARY TEAM

The heart failure team is comprised of a number of players. The lines of authority and communication among these people should be agreed on and incorporated into the program plan. Good communication is essential among the team members and the patient.

The primary care physician (PCP) is the anchor of the team, the person with whom patients have the strongest relationship, and the person who orchestrates care decisions that the other team members carry out. The PCP traditionally controls access to specialists. In a heart failure disease-management program, the PCP also plays this role, with the help of algorithms and protocols to improve outcomes. PCPs provide most of the care for patients with heart failure. Even in the hospital, cardiologists care for fewer than one-third of all patients admitted for heart failure. In fact, the cardiologist may refer patients to the PCP after guideline recommendations are implemented. In this way, patient referrals move both to and from specialty and primary care physicians.

The cardiologist is important for the management of patients with particularly difficult problems, such as those with multiple hospital admissions over a short period. As cardiologists who specialize in heart failure are still relatively rare, networks should be developed that allow PCPs or general cardiologists ready access to this additional consultation resource.

The heart failure specialist can be instrumental in developing and updating the clinical practice guidelines or care pathways used in the outpatient setting by the PCP. In helping develop the protocol, heart failure specialists should assist in interpreting and communicating published guidelines and ensure that the program is research-based and aggressive and provides the best opportunity to improve outcomes. Heart failure specialists generally have much experience in the aggressive care of very advanced heart failure syndromes, as the cornerstone for their proaction is usually patient referral for heart transplantation. They are more likely to promote options such as experimental drugs or emerging surgical procedures that might be suitable for very ill patients. Patients with advanced heart failure who wish to prolong survival should be referred to a team specializing in heart failure. This team will assess suitability for advanced heart failure therapies and can use palliative care where consistent with the patient's goals of care [10].

The cardiac nurse is used in many successful programs to assist in patient management [116]. In one inpatient program, total hospital costs were significantly lowered and length of hospital stay decreased in the year after a nurse was added to the team. In two hospital-based studies, patient education that included one-on-one, one-hour heart failure education delivered by cardiac nurses decreased subsequent hospitalization compared with usual care [117; 118]. Cardiac nurses have also been incorporated into programs at cardiomyopathy clinics, and reported outcomes have been good. In an aggressive, nurse-assisted management program, outpatient visits and communication increase, whereas hospital readmission rates decrease 33% [119]. Improvements in self-care knowledge and home-care behavior are credited.

Other team members include emergency medicine specialists, pharmacists, nutritionists, dieticians, cardiac rehabilitation personnel, social workers, home healthcare personnel, and palliative care specialists [120].

PROVIDING SERVICES TO PATIENTS

After the target population has been identified and the services or scope of the heart failure clinic have been decided, the next issue is how to provide these services to the patient population. One of the most common ways to manage patients with heart failure is through direct contact, predominantly by telephone. Nearly one-half of the surveyed clinics in the United States reported telephone contact as the primary method of patient management [19]. Such contact can be initiated either by the staff of the heart failure clinic or by the patient. In the former case, an initial call is usually made to patients soon after a hospital discharge, with the goals being determination of stability, understanding of medication changes, and cooperation with the current medical regime. This entails a transfer of information from the inpatient physicians and nursing staff to the heart failure clinic personnel. In some situations, heart failure clinic nurses actually visit patients in order to provide the continuity required for transition into the outpatient setting.

Beyond the initial telephone call, the role of the heart failure clinic often varies considerably. In some cases, a telephone call is made at fixed intervals, during which patient weight, symptoms, and problems are noted. These are often relayed to the appropriate physician for further action. In some instances, nurses and physicians have developed treatment algorithms or orders to be followed in various common clinical scenarios such as weight gain or leg edema. The additional follow-up actions usually depend on the teamwork and experience of the heart failure clinic staff.

Another development in telephone management has been computerized screening for patients at risk for further decompensation. In these systems, daily telephone calls may be initiated by the patient. Often, contact is initiated when a set of vital signs, such as weight, blood pressure, heart rate, and oxygen saturation, are measured at home. The home actions are transmitted via the patient's telephone line, usually to a central monitoring station. Limits for the various measurements are preset, and deviation usually triggers direct patient contact or notification of the heart failure clinic personnel for further action.

Because the average hospital has more than 500 primary heart failure admissions annually, perhaps one of the most difficult tasks is identifying which patients should be targeted for the heart failure clinic [19]. Ideally, some strategy should be directed at improving the outcome of all patients with heart failure as well as those with asymptomatic left ventricular dysfunction and those at risk for the development of heart failure. However, most clinics focus on the patient with overt, symptomatic advanced heart failure. Increasingly, patients admitted to a hospital with heart failure have very advanced symptoms and poor prognostic markers and, hence, are likely to be readmitted. In fact, readmission rates for these patients at 30 and 60 days approach 30% to 50% [121]. Also, because databases of financial information are found predominantly within medical institutions, outcomes regarding hospital length of stay and readmission are often the easiest to track. Some heart failure clinics are able to work closely with emergency departments,

which are the source of most hospital admissions for heart failure. In most cases, triage, treatment, and release are arranged by the heart failure clinic. This is obviously a good opportunity to enroll patients into the clinic population.

Readmission after hospitalization for heart failure is common, estimated at 25% at one month within the Medicare population [122]. Reduction in heart failure hospitalizations is an appropriate goal for treatment modalities and quality improvement strategies because hospitalization impacts adversely on both sides of the cost-effectiveness equation. On the cost side, hospitalization is the principal component of the high cost of care for patients with heart failure, representing 70% to 75% of total costs. On the effectiveness side, hospitalization may represent a failure of treatment, a progression of disease severity, or the elusiveness of effective interventions to prevent unnecessary readmissions. All scenarios detract from the patient's overall quality of life [122; 123].

As pharmacologic treatments continue to reduce mortality rates in heart failure, reduction of hospitalization frequency emerges as an increasingly important therapeutic goal. In the practice setting, physician adherence to prescription recommendations and patient compliance represent important goals in an effort to improve clinical outcomes, including reduction in heart failure hospitalizations.

To illustrate this, a study done in Portland, Oregon, at the Oregon Health Sciences University, evaluated the clinical and cost outcomes of care provided by their university-based heart failure outpatient management program [124]. Evaluation of the study showed success of the program intervention in reducing hospitalization and emergency room visits and in improving patients' quality of life and functional status. The improved clinical outcomes should be attributed to the comprehensive management strategies provided by specialized physicians and nurses that allowed for close symptom surveillance; timely interventions, such as augmentation of drug therapy; and promotion of patients' adherence to medical regimens and self-care recommendations.

The positive effect of the program intervention might be caused in part by an optimized medical regimen, such as the use of a more aggressive ACEI dosage, initiation of beta-blockers, and the approach of pre-emptive hospitalization in two-thirds of hospital events after referral. The study also showed that a comprehensive heart failure management program should be designed to care for patients in the outpatient setting before an episode of decompensated heart failure that required emergent hospitalization. This implies that hospitalization, the most costly intervention, should be managed and integrated prospectively into the care paradigm, rather than being a reactive, uncontrolled patient safety net resulting from a failure of the care process.

This study also described their process of pre-emptive hospitalization, which is any admission by the heart failure care team that avoids patient-initiated emergency room visits or home ambulance calls. Pre-emptive hospitalization was a proactive hospital admission for a patient exhibiting progressive decompensation despite a variety of measures in the outpatient setting (i.e., increased doses of diuretics, forced bed rest, urgent fluid and/or sodium restriction, more frequent clinic visits). The care team observed a marked reduction (72%) in emergency department visits [124].

Patient education was another important intervention. This study was the first that examined the pre- and post-program differences in the patient's knowledge of an adherence to self-care recommendations. At six months after referral, a significant improvement was shown in patients' knowledge regarding daily weight monitoring, importance of restricting dietary salt intake, and contacting providers if experiencing a sudden weight gain. However, the study members did not observe any changes in patients' self-reported adherence to dietary salt intake restriction and medical dosage compliance. This study showed improvement in patient quality of life after three and six months as measured by the Minnesota Living with Heart Failure Questionnaire, NYHA functional classification, fatigue and dyspnea score, and patient global assessment. There was also a reduction in risk of hospitalization, emergency department visits, and reduced expenditure [124].

In a landmark study conducted at one Veterans Affairs (VA) facility, a marked decrease in hospital days and healthcare costs was demonstrated. Total estimated outpatient cost increased 200%. However, because inpatient costs are much higher than outpatient costs, the net result was a 75% decrease in total patient cost. One large VA facility in the Midwest has had a nurse-managed clinic for patients with heart failure for the past 19 years. Successful outcomes include a dramatic reduction in readmission to the hospital at this institution [125].

At the initial visit, patients are encouraged to bring a spouse, family member, or significant other. The patient is given an explanation of his or her disease in layman's terms and has an opportunity to ask questions. The patient is also informed of the procedure for obtaining prescriptions through the clinic. Heavy emphasis is placed on obtaining a scale, the method of daily weighing, and the importance of knowing the target weight.

On subsequent visits, the patient's physical and psychosocial statuses, as well as the ability to self-monitor his or her condition, are assessed. Assessment by the nurse of the patient's ongoing ability to self-monitor is critical to the success of this model. Some questions asked of the patients on successive visits are:

- How have you been feeling?
- Have you had any shortness of breath? If so, doing what?
- How much work are you able to do?
- What are your average weights since the last visit?
- Are you having any problems with your medications?

Frequently, with the patient's help, diuretics will be titrated to treat fluid retention. It is not uncommon to give a bolus dose of a diuretic, and then have the patient closely monitor his or her weight at home. Telephone calls are made daily for a few days to check with the patient, and diuretics are prescribed accordingly. Patients are encouraged to report increased weight and symptoms at the onset to avoid hospitalizations.

TREATMENT PLAN

EVALUATION

Patients with poorly controlled heart failure require careful assessment at each visit [10]. The initial visit should focus on evaluating the type and cause of cardiomyopathy and excluding noncardiac diagnoses. Chest x-ray is a useful initial diagnostic test [10]. Symptoms of heart failure vary depending on the cause. Patients with systolic heart failure usually present with classic early symptoms of orthopnea and paroxysmal nocturnal dyspnea. Symptoms can become more subtle as left ventricular dysfunction worsens. Patients with diastolic heart failure (normal left ventricular ejection fraction, but impaired filling of the ventricle) are likely to present with exercise intolerance, dyspnea, and fatigue. Patients with cardiac amyloidosis may present with dyspnea, fatigue, fluid buildup in the abdomen and legs, and difficulty lying flat at night [126]. All patients with suspected heart failure should undergo a thorough physical examination and electrocardiography. Patients with suspected cardiac amyloidosis should be screened for serum and urine monoclonal light chains. Bone scintigraphy should be performed to confirm the diagnosis [10]. The presence of an S3 gallop and Q waves suggests systolic heart failure due to coronary artery disease, but clinical criteria alone are often insufficient for diagnosis. An S3 gallop increases with volume overload. Thus, objective assessment of the left ventricular ejection fraction using echocardiography or radionuclide ventriculography is usually necessary to determine appropriate treatment. Echocardiography is preferred because it can help evaluate diastolic as well as systolic dysfunction. It is also more effective in evaluating valvular dysfunction, which is often associated with cardiomyopathy. Patients who present with symptoms that are compatible with heart failure should be evaluated for disorders that may cause similar symptoms [10]. Complaints of fatigue and dyspnea on exertion should prompt an ongoing differential diagnosis, including chronic obstructive pulmonary disease, asthma, hypothyroidism, anemia, and chronic infections or inflammatory diseases. Heart failure

can be particularly difficult to diagnose in patients with lung disease, who may present with abnormal lung sounds and nocturnal worsening of symptoms that seem to be caused by heart failure [127]. The importance of monitoring serum potassium levels should be stressed due to the risk for hypokalemia or hyperkalemia.

Jugular venous pressure should be assessed with the patient sitting up at a 30- or 45-degree angle. Although jugular venous pressure can be difficult to interpret on initial examination, it is often the only reliable indicator of volume status in patients with chronic heart failure [10]. Hepatojugular reflux can also be assessed at each visit. Application of constant pressure over the liver causes a transient rise in pressure in the neck veins for a few cycles, followed by a return to normal in most patients.

The presence of crackles in the lungs during auscultation is usually evidence of pulmonary edema, and treatment with diuretics and afterload reduction should be instituted until the cause is clearly shown to be lung disease or another disorder.

Weight

Among patients with heart failure, weight has been referred to as the fifth vital sign; however, it might qualify as the first vital sign in these patients. Both the clinician and the patient should know the patient's optimal weight and assess it at each visit [10; 127]. Fluid retention is a significant symptom of heart failure. Patients are instructed on the importance of using the same scale to weigh themselves every day. Patients are advised to weigh themselves on a regular basis to monitor weight gain (preferably as part of a daily routine). In the case of a sudden, unexpected weight gain of >2 kg in three days or less, the patient should alert a healthcare provider and adjust his or her diuretic dose accordingly [46].

Smoking

Smoking should always be discouraged, despite the lack of evidence showing decreased risk of heart failure with smoking cessation [10]. The use of smoking cessation aids may be encouraged and may include nicotine replacement therapies [46].

Exercise

Conventional wisdom once held that exercise was contraindicated in patients with heart failure, but studies have found that bed rest and limited activity are detrimental to exercise tolerance and aerobic capacity. Moreover, it has been shown that even patients with a severely reduced left ventricular ejection fraction can improve their exercise capacity with appropriate training and cardiac rehabilitation [127]. In a major trial of exercise and heart failure, exercise training was associated with a reduction in cardiovascular mortality or hospitalizations [128]. A cohort study of 886 patients with heart failure from the National Health and Nutrition Examination Survey found that physical activity had a protective effect on prognosis, particularly among those with sedentary lifestyles [129].

Included in the treatment plan for heart failure in eligible patients is some time for exercise or regular physical activity [10]. Most patients in the clinic are able to exercise by walking. If patients have not been exercising at all, they begin by walking one to two blocks three times per week. Gradually, they increase their distance and time. They use symptoms of shortness of breath and fatigue as their guide to increase or decrease exercise. The benefit to the patient is not only physical but psychologic as well. On initiation of exercise, self-confidence, self-esteem, and stamina can improve [130]. After many years of restricting patients with heart failure from aerobic exercise, researchers have demonstrated that aerobic exercise training in patients with heart failure results in improved exercise duration, less fatigue, faster pace of activities, and improved general well-being. Given the threat of complications related to increased myocardial oxygen demand in the face of isometric exercise, patients are usually counseled to avoid lifting significant weight (>20 lbs) or performing exercises that cause strain (e.g., performing a Valsalva maneuver). Because inactivity leads to decline in function, exercise tolerance should be assessed at each visit for patients who are not responding well to treatment.

Prior to beginning an exercise program, assessment and documentation of NYHA functional classification are recommended to determine eligibility for treatment. In ambulatory patients, performing a cardiopulmonary exercise test or six-minute walk test is reasonable to assess functional capability [10].

Sexual Activity

Sexual problems are well documented in the patient with heart failure and should be carefully assessed by the practitioner. Fears about physical exertion or symptoms may contribute unnecessarily to sexual difficulties. Sexual practices may have to be modified to accommodate patients with limited exercise tolerance, and practitioners should be proactive in raising this topic to avoid unnecessary anxiety on the part of patients or their partners [131]. Of course, it is not possible to dictate guidelines, but referral to counseling may be beneficial [46].

Medications

Adherence to treatment is promoted by the establishment of a mutually authored treatment regimen. Medications are reviewed with the patient, including administration schedule, strategies for dealing with a missed dose, and how to titrate a medication as applicable. The importance of each medication is discussed.

Patients should be taught the name of each drug and its purpose, dosage, frequency, and significant side effects. For example, patients who take beta-blockers should be told that they may experience fatigue, light-headedness, or dizziness. They should be further instructed that the beta-blocker will be up-titrated slowly, as tolerated. Patients who are not properly instructed about the purpose and side effects of beta-blockers may stop taking this medication because they think that their heart failure has worsened. In addition, patients should be instructed to bring all of their medications with them to each office visit. This serves two purposes. First, information about each drug can be reviewed and the patient's knowledge can be assessed. Second, the practitioner can identify omissions, duplications, confusion about drug doses, and drug interactions. Patients should be asked about over-the-counter and alternative medications they may be taking. Alternative medications should not be taken without first consulting the healthcare team, and nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided completely because they can lead to renal dysfunction and renal failure. A written medication schedule is strongly recommended to reduce the adverse effect of polypharmacy on patients' daily lives, patient compliance, and the potential for drug interactions. If the regimen is complex, the practitioner should review it to determine whether medications can be changed to single-dose medications. Patient history should include an assessment of the degree to which medications are disruptive to a patient. Medication schedules can then be constructed to minimize their impact on patients' daily activities and sleep schedules. A medication schedule may minimize the potential for drug interactions. A written medication schedule is also useful if the patient requires sudden hospitalization [131].

There is no documented evidence of negative effects of immunization in patients with heart failure. Immunization for influenza is widely and safely used. However, the following drugs should be avoided or used with caution when co-prescribed with any form of heart failure treatment [46]:

- NSAIDs and coxibs
- Class I anti-arrhythmic agents
- Calcium antagonists (verapamil and diltiazem)
- Tricyclic antidepressants
- Corticosteroids
- Lithium

Alcohol

Alcohol consumption may have a detrimental effect on patients with heart failure. Acute ingestion depresses myocardial contractility in patients with known cardiac dysfunction. Complete abstinence is essential in patients with alcoholic cardiomyopathy [46]. The use of alcohol should be discouraged in all other patients with left ventricular dysfunction. Patients who refuse to abstain should limit their alcohol intake to no more than one drink per day [127].

Patients should be counseled prior to enrollment in the clinic to change their present behaviors in order to promote healthy outcomes. If a person has a history of alcohol abuse, tobacco use, or poor dietary habits, each problem is addressed separately; alcohol abuse problems are addressed first [125]. This is particularly important in cases of alcoholic cardiomyopathy; these patients should be advised to abstain from all alcohol intake. For all other patients, moderate alcohol intake (e.g., one alcoholic drink per day) is permitted and may actually reduce heart failure risk [46].

Diet

Dietary habits should be discussed with the patient and his or her family. Many deny adding salt to food, but they often do not realize that many foods are inherently high in salt. A 2- to 3-gram/day sodium diet is usually recommended; however, there are no trials to support this level of restriction in patients with heart failure. Furthermore, sodium restriction can result in poor dietary quality, with inadequate macronutrient and micronutrient intake [10]. Depending on need, patients are given a list of common foods that are high in salt. Together, a treatment plan is devised in which the patient is allowed to have some preferred salty food on a weekly or monthly basis. Thus, the patient does not feel deprived and is more likely to follow the prescribed diet. Patients with well-controlled heart failure are usually able to tolerate the occasional addition of a salty food to their diet, whereas those with advanced heart failure may experience signs of congestion, fluid retention, and dyspnea on ingestion of even a very minimal amount of salty food. Dietary instruction should take into account ethnic preferences and may require individualized counseling by a dietitian. Although some patients with heart failure are obese, other patients with advanced heart failure experience a syndrome of chronic wasting, which can be exacerbated by unnecessary dietary restrictions. Frequent, small meals may combat the effect of anorexia caused by congestion of the gastrointestinal tract. Instructions on fluid control should be provided to patients with advanced heart failure, with or without hyponatremia. The ideal amount of fluid restriction remains unclear; in practice, a fluid restriction of 1.5–2 L/day is advised in advanced heart failure [46].

Socialization

On initiation of a treatment plan, patients are asked if they have any hobbies, if they belong to clubs, and how they socialize. Due to the recent decline in the progression of the disease, an increasing number of patients are able to work until they are in the advanced stages of this syndrome.

Depression

Depression in heart failure contributes to a decreased quality of life and inability to maintain activities of daily living [132]. Among patients with heart failure, those who are hospitalized report the highest incidence of depressive symptoms (78%) [133].

Assessment for depression in patients with heart failure is just as essential as the assessment of other cardiovascular risk factors [134]. Practitioners should not dismiss mild depression, as its presence is well documented in heart failure intervention trials [135]. Evidence supports a relationship between depression and poor heart failure outcomes, including increased frequency of hospitalizations, worsening quality of life, and increased mortality, which further supports to the need for depression screening in patients with heart failure [10; 135].

PATIENT OUTCOMES

As noted, enrollment in heart failure clinics has resulted in a significant reduction in readmissions to the hospital, as well as emergency department visits. Despite the fact that traditional aspects of disease progression, such as mortality and readmission, are important and useful outcomes with which to judge the efficacy of a heart failure management program, patient-centered outcomes, such as functional status and quality of life, are increasingly recognized as important markers of healthcare quality. The term "quality of life" has come to be perceived as synonymous with patient-rated, nonclinical aspects of health status, whereas functional status is defined as the ability to exercise measured by NYHA classification and peak oxygen consumption. Often, these terms are used interchangeably, and progress or deterioration of one can directly affect the other.

Knowing the patient's quality of life and functional status at the onset of a new heart failure intervention, such as enrollment in the heart failure clinic, is helpful in assessing the ongoing progress of each patient. Fatigue, a major symptom of heart failure, is sometimes difficult to measure. Drugs such as ACEIs and beta-blockers can help to improve levels of fatigue. Fatigue can also be influenced by feelings of depression related to chronic illness [125].

The ACC/AHA/HFSA asserts that in patients heart failure and suspicion of sleep-disordered breathing, a formal sleep assessment is reasonable to confirm the diagnosis and differentiate between central and obstructive sleep apnea.

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Level of Evidence: 2a (Moderate recommendation based on moderate-quality evidence from one or more randomized controlled trials)

COMPLIANCE

Noncompliance with heart failure treatment plans was found to be common and appeared to increase as heart failure progressed. There are many reasons that patients may not comply with a therapeutic regimen. Lack of knowledge, poor motivation, decreased understanding, lower perceived self-efficacy, forgetfulness, and decreased support from family and other caregivers have been identified as factors that contribute to noncompliance. Patients may not comply with a prescribed regimen because they are unconvinced of the benefits of doing so or because they perceive that the side effects or inconveniences of following the regimen outweigh any benefits. If cost is a factor in noncompliance, suggestions for lower-cost medications or financial assistance programs should be provided. Another important factor that contributes to patient noncompliance and rehospitalization for worsening heart failure is inadequate discharge planning and follow-up after discharge.

The management of heart failure in elderly persons is often made more challenging by the presence of multiple coexisting problems. These factors contribute to the increased vulnerability of elderly patients to noncompliance and rehospitalization for heart failure and include:

- The presence of comorbidities such as diabetes, chronic lung disease, and stroke
- Polypharmacy
- Financial concerns
- Physical and cognitive limitations
- Inadequate social support and social isolation
- Depression and anxiety

Clinicians who do not consider these factors when caring for elderly patients with heart failure can contribute to patient noncompliance.

A few studies have examined the role of healthcare provider compliance with heart failure practice guidelines and the impact on patient outcomes [109; 110]. Despite the publication of consensus guidelines that established standards for heart failure medical therapy, many patients are still not prescribed ACEIs, do not receive them in adequate doses, and/or are prescribed drugs that may have deleterious effects on heart failure. The use of ACEIs for the treatment of heart failure in the community setting has increased, but the use has remained below recommendations in practice guidelines. More cardiologists than noncardiologists were found to conform to published guidelines for the management of patients with heart failure. Specifically, more cardiologists than generalists were likely to use ACEIs for the treatment of mild, moderate, and severe heart failure and titrated doses proved to be efficacious in clinical trials. Other studies have found that patients who were referred to heart failure specialists had fewer hospitalizations.

FUTURE OF HEART FAILURE TREATMENT

HEART FAILURE CLINICS

A major challenge is to identify the combination of interventions within a given program that is effective. Because there have been no studies that compare the relative effectiveness of different programs or that compare individual components or combinations of components within programs, there remain several unanswered questions. For example, is a truly multidisciplinary team necessary, or is it sufficient for teams of nurses and physicians to manage patients? Until there is research available, identification of the components common to successful programs that are adaptable to a variety of communities and settings can provide guidance to clinicians. Optimization of medical therapy based on consensus heart failure guidelines is an important aspect of care for heart failure programs.

In making decisions about which components to include in a heart failure program, the characteristics of the target population should be examined. For example, if the heart failure population to be targeted consists of very elderly patients, a program that includes some component of home care is likely to be more successful given the mobility and transportation difficulties experienced by many elderly patients. In addition, elderly patients are a more vulnerable population due to often unresolved social and financial issues. The inclusion of mechanisms to address these issues is important to the success of a program.

Another challenge is determining how to implement a heart failure clinic outside an academic center, as most research has been done in academic medical centers. Many of the heart failure programs were formed in academic medical centers to conduct pharmaceutical trials or to manage patients before and after heart transplantation. Community-based programs are trying to provide the intensive care these patients require, although reliable sources of reimbursement for the commitment of specialized nursing are just beginning to become available. Implementation of a heart failure clinic in a community setting not associated with an academic medical center depends on guidance from committed, experienced clinicians. Cardiologists and experienced cardiovascular advanced practice nurses manage many successful heart failure programs in a variety of communities across the United States.

An integral part of any heart failure program is evaluation, and every program should include a plan for evaluation of its effectiveness. Evaluation of the impact of a program allows for refinement to improve program effectiveness and provides data when seeking reimbursement for a program from managed care organizations and insurance companies [131].

NURSING IMPLICATIONS

Heart failure clinics managed by nurses can take a variety of approaches. Nurses can manage these patients in close collaboration with a physician, as part of an interdisciplinary team, or as primary care providers. Outcomes in these clinics are significant and include a dramatic cost savings. Despite increased outpatient costs, initial time spent with the patient and his or her family in the outpatient setting can result in a decrease in inpatient admissions. Nurses, by their ability to address the myriad concerns of this population, have demonstrated that the total care given to the patient ultimately has the potential to increase patient quality of life and to decrease unnecessary readmission for heart failure.

The term "heart failure" has a negative connotation. It is important for the nurse caring for patients with heart failure to convey an attitude of hopefulness, even during the advanced stages of the disease. It is imperative that nurses remember that their beliefs about adherence will influence the way they interact with the patient. If a nurse believes that older persons or those with little education will not comply with their treatment, that belief will be conveyed nonverbally to the patient and may influence the patient's comprehension. Change is always possible, but it is built on honesty. Finally, the care of patients with heart failure should include those close to them. Including these significant others not only identifies potential problems before they occur but gives the patient a broader base of support. In essence, to treat heart failure effectively, a team and a plan are necessary. Although some may say such an approach is "cookbook medicine," the proof is in the outcomes. Studies have shown that patients treated in formal programs have lower hospitalization rates, fewer emergency visits, and a higher quality of life, functional status, and level of satisfaction with their care. With a team in place, work may be delegated.

Nurses keep in contact with the patients at home on a regular basis, heading off problems before they become crises. Heart failure specialists and others are available if their input is necessary. With a formal plan, adherence to evidence-based guidelines can be guaranteed. A program can, therefore, be proactive instead of reactive, concentrating on keeping patients healthy, instead of dealing with acute exacerbations. A team approach to heart failure management can be implemented in most traditional or managed-care outpatient settings [120].

Regardless of the methods utilized in identifying, communicating with, and treating patients with heart failure, some indicators of the success of interventions are required. Financial outcomes are frequently the easiest to obtain and measure. Seventy-two percent of heart failure clinics employ outcome measures other than financial data for their patients. Additionally, quality of life is measured in 58% of patients attending heart failure clinics, as this is perceived to be an important goal of a program treating patients with advanced disease [19].

Perhaps one of the most important requirements of a heart failure clinic is a suitable medical information system to allow tracking of key measurement parameters. The data set should also serve as an electronic medical record capable of monitoring frequent changes in medications and adverse reactions. A reporting feature of the software is also important to provide an up-to-date summary of information and testing should patients present to the emergency department or require hospital admission. Remote access enhances the value of the data set, particularly when the clinic personnel are limited. Few of the commercially available electronic records are ideal for the management of chronic heart failure, but this will probably change as the need becomes more apparent.

PREVENTION

Coronary artery disease has emerged as the major etiologic factor in the development of heart failure in the United States and other developed nations. As techniques used for percutaneous and surgical revascularization continue to improve, the ability to protect myocardium from ischemia and/or infarction can only be expected to increase. An exciting possibility is the potential for delivery of growth factors, such as vascular endothelium growth factor or basic fibroblast growth factor, to areas of myocardium jeopardized by insufficient blood flow as a result of atherosclerotic coronary artery disease. Coronary artery growth factor therapy is an intriguing possibility as a means of protecting myocardium and preventing heart failure.

Treatment of risk factors for coronary artery disease should be a high priority. Use of a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, simvastatin, in the 4S trial not only improved survival but also significantly reduced the future risk of developing heart failure. Another area of concern is the treatment of hypertension. When hypertension is treated, the impact on preventing heart failure is substantial. In the Systolic Hypertension in the Elderly Program (SHEP), treatment of elderly patients with systolic hypertension resulted in a 49% reduction in the likelihood of developing heart failure [136]. Many trials have shown that control of hypertension reduces the risk of heart failure. Although the magnitude of the benefit varies with the patient population, target blood pressure reduction and effective hypertension treatment invariably reduces heart failure events [10]. The AHA/ACC/HFSA guideline provides recommendations for the management of other risk factors for heart disease including, iron deficiency, anemia, sleep disorders, and type 2 diabetes [10]. These chronic conditions complicate the management of heart failure and can have a significant impact on its prognosis [10].

For select interventions, the AHA/ACC/HFSA guideline includes value statements with high-quality published economic analysis [10].

It will take a concerted and sustained effort by numerous parties, including the government, pharmaceutical companies, consumer and physician groups, and enlightened health maintenance organizations, to bring about change in this area. If risk factor management can be improved, it would have a substantial effect on the incidence of heart failure and its clinical sequelae.

What is needed is a means of reliably and inexpensively screening a population at risk for early indicators of cardiac dysfunction. Some evidence suggests that the family of natriuretic peptides (i.e., ANP and BNP) that are released from the heart in response to stretch may be useful to detect evidence of incipient heart failure. One study found that among patients at risk of heart failure, BNP-based screening and collaborative care reduced the combined rates of left ventricular systolic dysfunction, diastolic dysfunction, and heart failure [137]. Results such as these could potentially lead to routine screening of populations at risk with a blood test to help select patients for early initiation of neurohormonal blockade. The ACC/AHA/HFSA 2022 update supports the use of BNP-based screening for initial diagnosis, risk stratification, early intervention, and prevention [10].

In addition to earlier initiation of neurohormonal blockade during the preclinical phase of heart failure, there are several promising neurohormonal blockers that are currently under investigation. Endothelin is an extremely potent vasoconstrictor. It also promotes hypertrophy of cardiac myocytes and stimulates other neurohormonal systems. Circulating endothelin levels have been shown to be elevated in patients with heart failure [138; 139].

In experimental animal models of heart failure, the chronic administration of endothelin receptor blockers improves cardiac function and hemodynamic variables. Other endothelin blockers are in development and clinical trials are either planned or under way with several of these drugs.

SURGICAL TREATMENT

New surgical techniques and improvements of more established therapies designed to improve or replace cardiac function have been developed over the past decades. These techniques fall into three major categories: conventional surgical treatment applied to patients not previously approached, attempts to augment intrinsic cardiac function, and cardiac replacement strategies.

In the first category are revascularization and mitral valve surgery. The major emphasis in the former has been to better define which patients with severe left ventricular dysfunction are likely to respond to aggressive and complete revascularization.

Four major approaches to augmentation of diseased myocardium have been instituted—three clinically and one still in animal models. These include cardiomyoplasty, left ventriculectomy, transmyocardial laser revascularization, and myocyte/myoblast cell transplantation. The newest and potentially most exciting technique to rehabilitate diseased and dysfunctional myocardium is muscle cell transplantation using either skeletal myoblasts or fetal cardiomyocytes. Finally, cardiac replacement strategies have continued to evolve and are anticipated to bring continued new approaches to the treatment of end-stage heart failure. A number of new immunosuppressive agents that are more efficacious and less toxic have been released for clinical use or are in clinical trials. More than 5,000 heart transplants are performed annually worldwide, while the estimated need for organ replacement is, at minimum, 10 times that number [140].

The expanded use of permanent mechanical VADs is becoming an important part of the treatment of heart failure. According to the Organ Procurement and Transplantation Network, improvements in VAD technology have led to one-year survival rates approaching those of heart transplant [141]. Devices have been extensively studied in the setting of bridging to transplantation. Current devices are still bulky, require a sternotomy, and are energy inefficient given the assumed need of pulsatile flow.

STEM CELL THERAPY

In the last several years, the understanding that regenerative processes exist at the level of the myocardium has placed stem cell research at the center stage of cardiology. Through cellular therapies, the concept of "growing" heart muscle and vascular tissue and manipulating the myocardial cellular environment has revolutionized the approach to treating heart disease.

Cell transplantation is the first therapy designed to treat the underlying injury in heart failure—cardiomyocyte and vessel cell death—and bring us closer to the ambitious goal of myocardial regeneration. Since 1998, when functional repair after injection of autologous skeletal myoblasts into the injured heart was first reported, a variety of cell types have been proposed for transplantation in different stages of cardiovascular disease. It now appears clear that cell-based cardiac and vascular repair is feasible, both early and later in the disease process. However, many questions about the technology remain. Cardiac regeneration, literally regenerating contractile cardiac muscle, functional vasculature, and electrical conductance in a fibrous, dilated, and underperfused scar, is the ultimate goal. In summary, cell-based cardiovascular repair offers unprecedented potential to treat the underlying injuries associated with cardiovascular disease and ultimately perhaps reverse the disease process [142; 143].

GENE THERAPY

Using modern techniques of linkage analysis, investigators have uncovered genetic mutations that result in a number of inherited cardiovascular diseases, including hypertrophic cardiomyopathy. Genetic variants have been implicated in 25% to 40% of patients with dilated cardiomyopathy with a positive family history but also in 10% to 30% of patients without a recognized family history [10]. Progress in uncovering point mutations that lead to dilated cardiomyopathy should help reveal intracellular pathways and mechanisms that give rise to the heart failure phenotype. Phenotype and family history are important for identifying patients for whom genetic testing is most likely to yield clinically relevant information [10].

Progressive changes in response to injury lead to structural and functional changes that are the cause of heart failure in most patients. The likelihood and rapidity of the development of heart failure appears to vary greatly among patients, suggesting that there may be genetic modifiers of the rate of progression. The AHA/ACC/HFSA 2022 guideline recommends genetic screening and counseling in first-degree relatives of select patients with either genetic or inherited cardiomyopathies. The goals of such screening are early detection and intervention to decrease heart failure progression and sudden death [10].

The use of polymerase chain reaction amplifications of DNA obtained from white blood cells makes analysis of the presence of various polymorphisms relatively easy to accomplish. The application of this technique prospectively in a large population should help uncover associations between polymorphisms and changes in the rate of progression of disease. This information will help to not only provide insights into mechanisms of heart failure but also provide therapeutic targets for intervention [136].

JOINT COMMISSION GUIDELINES FOR HEART FAILURE

The Joint Commission Certification Program for Disease-Specific Care (DSC) provides a comprehensive evaluation of disease or condition-specific services. The Joint Commission's certification is based on an assessment of compliance with relevant standard and criteria, the effective use of clinical guidelines, and outcomes measurement [144].

There are two stages of DSC certification programs. The first stage is comprised of collection and analysis of four or more performance measures defined by the facility, two of which are required to be related to or identified in clinical practice guidelines for that program [144]. The second stage involves adoption of standardized performance measures as defined by the Joint Commission. Six core measures have been established by the Joint Commission for heart failure center certification [145]:

- Beta-blocker therapy prescribed for left ventricular systolic dysfunction (LVSD): Beta-blocker therapy (i.e., bisoprolol, carvedilol, or sustained-release metoprolol succinate) is prescribed for patients with heart failure and LVSD. For the purposes of this measure, LVSD is defined as chart documentation of a left ventricular ejection fraction less than 40% or a narrative description of left ventricular systolic function consistent with moderate or severe systolic dysfunction.

- Post-discharge appointment: Patients for whom a follow-up appointment for an office or home health visit for management of heart failure was scheduled within seven days post-discharge and documented including location, date, and time.

- Care transition record transmitted: A care transition record is transmitted to a next level of care provider within seven days of discharge containing all of the following:
  - Reason for hospitalization
  - Procedures performed during this hospitalization
  - Treatment(s)/service(s) provided during this hospitalization
  - Discharge medications, including dosage and indication for use
  - Follow-up treatment and services needed (e.g., post-discharge therapy, oxygen therapy, durable medical equipment)
- Discussion of advance directives/advance care planning: Patients who have documentation in the medical record of a one-time discussion of advance directives/advance care planning with a healthcare provider.
- Advance directive executed: Patients who have documentation in the medical record that an advance directive was executed.
- Post-discharge evaluation: Patients who receive a re-evaluation for symptoms worsening and treatment compliance by a program team member within 72 hours after inpatient discharge.

In 2019, the Joint Commission, in collaboration with the AHA, began offering an advanced certification in heart failure [146]. This certification requires that organizations comply with current Joint Commission standards for disease-specific care and participate in the AHA's Get With the Guidelines heart failure registry [147].

CONCLUSION

As discussed, the economic and psychosocial effects of heart failure, a chronic and debilitating disease, are great. Although advances in the assessment and treatment of heart failure have been increasing, additional steps should be made to ensure that patients receive the most appropriate care, based on evidence-based guidelines and recommendations. One of the most feasible plans to decrease morbidity and mortality associated with heart failure is the implementation of heart failure clinics, which have the ability to address provision of services, patient education, follow-up plans, thorough evaluation, and establishment of a monitored treatment plan.

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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