Target Audience
This activity is intended for cardiologists, interventional cardiologists, internal medicine and primary care physicians, and other health care professionals engaged in the care of patients with heart failure.

Educational Objectives
After completing this activity, the participant should be better able to:
- Implement heart failure classification systems, such as the ACC/AHA stages or NYHA functional classification, in order to effectively stage patients and direct treatment goals
- Evaluate the role of biomarkers as prognostic indicators, and to monitor therapy for patients with reduced or preserved ejection fraction heart failure
- Implement pivotal study data for recently approved therapies for patients with heart failure
- Implement electricity and catheter-based therapies for heart failure patients who are appropriate candidates

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Advances in Heart Failure Management: Improving Outcomes With Innovation

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Heart failure (HF) is a chronic and complex disease entity with an enormous morbidity and mortality. Many of the therapies used in the management of HF were developed decades ago, but recently more novel monitoring and therapeutic strategies have emerged. The employment of these strategies may reduce morbidity and mortality in patients with HF. This article reviews the epidemiology of HF and some of the novel strategies developed to assess risk and monitor these challenging patients. It also discusses the evidence behind some of the newer treatments available that are recently included in the HF management guidelines. Various devices used in the treatment of HF, some of which remain investigational, are also discussed. Novel strategies for remote monitoring and new pharmacologic therapies may be useful in improving morbidity and mortality in patients with HF.

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KEY WORDS

Heart failure • Guideline-directed medical therapy • Device therapy • Mortality risk

Heart failure (HF) currently affects nearly 6 million patients in the United States alone; by 2030, this number is expected to increase to 8 million. In approximately 1 million hospitalizations, HF is listed as the primary diagnosis, and nearly one in four HF patients will be rehospitalized within 30 days of discharge. Additionally, the direct costs of HF are expected to more than double, from over $30 billion to $70 billion per year in 2030.[1] The lifetime risk for developing HF is one in five regardless of age[2]; with the continued aging of the population and improvements in the management of medical comorbidities, the incidence of HF is expected to continue to rise.[3]

The diagnosis of HF has important implications for prognosis. After diagnosis, survival estimates are 50% and 10% at 5 and 10 years, respectively; beyond risk for pump failure, left ventricular (LV) dysfunction is also associated with an increase in sudden death.[4] Clinically, the natural history of HF is a steady downhill functional decline punctuated by episodic exacerbations requiring hospitalization for management with partial, but incomplete, recovery with pharmacologic treatment. History of an HF hospitalization, the number of HF hospitalizations, and the shorter time to HF hospitalization are all associated with a high mortality in HF patients.

Despite advancements in the field, the impact of HF has continued to increase, and it is clear that improvements in the diagnosis, treatment, and management of HF are needed to offset the enormous morbidity and mortality associated with this complex disease process.

Classification of Heart Failure

The American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) define four stages of HF.[5] Stage A includes patients who do not have clinical HF, but are at high risk for developing HF because of comorbidities such as advanced age, diabetes, hypertension, and coronary artery disease. Stage B includes those with structural heart disease but without symptoms of HF. Those in Stage C have both structural heart disease and prior or current symptoms of HF, and those in stage D have refractory HF requiring advanced therapies or end-of-life care. Additionally, for those in Stage C and beyond, the ACCF/AHA classifies HF patients according to functional status using the New York Heart Association (NYHA) class structure, in which I means no limitation of physical activity and IV means a patient is unable to carry on any physical activity without symptoms (Table 1).

Patients with HF are typically divided into two broad groups: those with HF with reduced ejection fraction (HFrEF), defined as HF with an ejection fraction (EF) of $\leq$ 40%; and those with HF with preserved EF (HFpEF), defined as an EF $\geq$ 50%. Patients with an EF of 41% to 49% are in a borderline or mid-range category.[5,6] It is important for clinicians to be aware of HFpEF, because it is associated with a high morbidity and mortality, and accounts for half of the patients diagnosed with HF.

TABLE 1

Classification of Heart Failure

Stages of HF	NYHA Class
Stage A High risk for HF No structural heart disease or symptoms of HF	
Stage B Structural heart disease No symptoms of HF	NYHA class I No limitation of physical activity
Stage C Structural heart disease Current or prior symptoms of HF	NYHA class II Slight limitation of physical activity Ordinary physical activity results in symptoms of HF
	NYHA class III Marked limitation of physical activity Less than ordinary activity results in symptoms of HF
Stage D Refractory HF requiring specialized interventions	NYHA class IV HF symptoms at rest Unable to carry on any physical activity without symptoms of HF

HF, heart failure; NYHA, New York Heart Association.
Data from Yancy CW et al.[5]

There are no proven therapies for patients with HFpEF; however, this is an area of active research and, it is hoped we will have therapies aimed at the treatment of this important patient population in the near future. This review focuses on patients with HFrEF, for whom guideline-directed medical treatments (GDMTs) are available.

Characterizing the Patient With Heart Failure

Symptoms of Heart Failure

HF is identified clinically based on the presence of typical signs and symptoms on clinical history and physical examination. Dyspnea is the cardinal symptom of HF but is hardly specific for HF. Other congestive symptoms of HF include orthopnea (dyspnea when supine) and paroxysmal nocturnal dyspnea. When orthopnea is severe, patients may choose to sleep in a recliner or prop their heads up with multiple pillows rather than lie flat. A patient reporting paroxysmal nocturnal dyspnea may describe awakening abruptly in the middle of the night with dyspnea or a feeling of suffocation. Another entity that occurs in a congested state is bendopnea, a sensation of shortness of breath when bending down, which frequently occurs in the setting of venous congestion and a drop in cardiac output.[7] Other common symptoms of HF include edema, abdominal pain and/or distention, weight gain (or loss in advanced stages, so-called *cardiac cachexia*), fatigue, and right upper quadrant pain due to hepatic congestion. On physical examination, patients with HF may have jugular venous distention—one of the earliest and most specific signs for decompensated HF—hepatojugular reflux, lower extremity edema, crackles or wheezes on lung examination, and abdominal distention.

Comorbid Conditions in Heart Failure

On average, patients with HF have five medical comorbidities; three of the most common are hypertension, ischemic heart disease, and diabetes.[5] Such comorbidities are associated with an increase in morbidity and mortality associated with a diagnosis of HF. Given the interactions among medications used to treat HF and those used in the treatment of the numerous comorbidities, it is essential for clinicians to recognize these interactions and utilize the expertise of various specialists and/or clinical pharmacists in the management of these patients. Additionally, various GDMTs may be contraindicated in patients with certain comorbidities; for example, mineralocorticoid receptor blockers in those with chronic kidney disease.

> ***… various GDMTs may be contraindicated in patients with certain comorbidities; for example, mineralocorticoid receptor blockers in those with chronic kidney disease.***

Goals of Therapy for Patients With Chronic Heart Failure

When characterizing patients according to the ACCF/AHA stages of HF (Table 1) there are different goals of therapy and treatment strategies for each stage.[5] In patients with stage A HF, the goal of therapy is to reduce risk factors such as hypertension that are associated with the development of HF, to prevent ischemic events by risk-factor modification such as smoking cessation and treatment of hyperlipidemia, and to prevent development of LV structural abnormalities. In a patient with stage B HF who has structural heart disease, the goal of therapy is to prevent HF symptoms and prevent further LV remodeling using GDMT. In patients with stage C and D HF, the goal of therapy is to control HF symptoms, improve quality of life (QoL), and prevent hospitalization using GDMT. Additionally, in stage C patients, reduction of mortality is a therapeutic goal; in those with refractory stage D HF, it is important to establish end-of-life goals and whether they are candidates for advanced therapies such as transplant or mechanical circulatory support.

Risk Assessment and Monitoring Strategies

Risk stratification is an important component of the evaluation of patients with HF. It is important to communicate prognostic information to patients in an effort to motivate them to be vigilant of their symptoms and to improve adherence to GDMT and lifestyle recommendations; it is also important for clinicians, as it assists them in managing frequency of follow-up and referral for advanced therapies such as transplantation or mechanical circulatory support. Several clinical factors and laboratory measurements predict increased risk in patients with HF, including age, atrial fibrillation, diabetes, creatinine level, and B-type natriuretic peptide (BNP) concentration.

Biomarkers, of which BNP and N-terminal pro B-type natriuretic peptide (NT-proBNP) are the most extensively studied, play a role in the diagnosis and monitoring of patients with HF. Concentrations of BNP and NT-proBNP are higher in those with HF compared with those without HF and measurement of BNP or NT-proBNP is a class I indication that assists in the diagnosis and prognosis of HF.[5] BNP

and NT-proBNP levels correlate well with the degree of LV dysfunction and elevation in LV pressures; their concentrations also increase in the setting of valvular heart disease, arrhythmias, infiltrative cardiomyopathies, and acute coronary syndromes. It is important to note that there are noncardiac factors that increase the concentrations of BNP and NT-proBNP, as well (Table 2).[8] Lower than expected BNP and NT-proBNP concentrations may be found in patients with obesity, HFpEF, and right heart-predominant HF.

BNP and NT-proBNP concentrations provide prognostic information in patients with both acute and chronic HF. In a study of patients with acute HF, a baseline NT-proBNP concentration $>$ 5180 pg/mL was strongly predictive of death by 76 days (odds ratio 5.2; 95% confidence interval [CI], 2.2-8.1; $P < .001$).[9] Natriuretic peptides are useful in chronic HF as well; in the Valsartan Heart Failure Therapy (Val-HeFT) trial, an NT-proBNP level above 1078 pg/mL was predictive of mortality (hazard ratio [HR] 2.07; $P < .001$) and morbidity (HR 2.66; $P < .001$).[10]

The more novel biomarkers such as soluble ST2 (sST2) and galectin-3 have been studied in patients with both acute and chronic HF. Both have been given a class II recommendation in current practice guidelines for risk assessment in HF.[5] sST2 is a member of the interleukin-1 receptor family and is released under conditions of mechanical myocardial strain. The role of sST2 lies in its ability to prognosticate adverse events in both acute HFrEF and HFpEF. In acute and chronic HF, concentrations of sST2 predict worsening HF, rehospitalization, heart transplantation, ventricular remodeling, and death.[11] Galectin-3 is a biomarker associated with tissue fibrosis and LV remodeling. The prognostic ability of galectin-3 in the setting of chronic HF is more variable. Although biomarkers may provide useful information, it is important to interpret them in the context of the clinical picture.

TABLE 2

Non-cardiac Causes of Elevated BNP or NT-proBNP

Pulmonary	Pulmonary embolism Pulmonary hypertension Chronic lung disease Acute respiratory distress syndrome Sleep apnea
Neurologic	Subarachnoid hemorrhage Stroke
Endocrine	Hyperthyroidism
Organ failure	Liver failure Renal failure
Patient characteristics	Advanced age
Critical illness	Sepsis Burns
Other	Anemia

BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro B-type natriuretic peptide.
Data from Baggish AL et al[8] and Ibrahim and Januzzi.[46]

Multiple risk scores have been developed to estimate risk in patients with HF. One score that is widely used is the Seattle Heart Failure Model. It was developed from a cohort of 1125 patients and validated in five other patient cohorts (N = 9942). It includes clinical variables, GDMT, device therapy, and laboratory values, and is able to predict mortality/survival at 1, 2, and 5 years.[12] Clinicians enter these variables and calculate the score in patients using a calculator available online, as well as using an application available on most smart phones. It is not only important to assess HF patients' risk for adverse events, but also to assess their QoL. HF is a morbid disease and it adversely affects a patient's QoL; as such, it is important to objectively assess this in order to improve QoL, if possible. Additionally, assessment of QoL provides prognostic information in this patient population. One such tool to objectively assess a patient's QoL is the Kansas City Cardiomyopathy Questionnaire; additionally, it provides information regarding risk of HF hospitalization. Worse scores confer a substantially higher risk for HF hospitalization and death.[13]

Remote Monitoring

Longitudinal disease management, including routinized heart failure education, early post discharge support, and longitudinal nursing surveillance, is associated with improved clinical outcomes in HF.[14] Longitudinal monitoring of HF patients is typically accomplished through periodic surveillance of weight, symptoms, and vital signs. Although telemonitoring strategies are occasionally employed to supplement clinic-based follow-up and provide more intensive day-to-day surveillance, this strategy has not proven to be effective in routine HF management. Most recently,

The Better Effectiveness After Transition-Heart Failure study randomized 1437 patients hospitalized for HF to home health versus usual care; only 83% of the intervention arm used the telemonitoring equipment. There was no significant difference between the two arms in terms of 30- and 180-day readmission rates; 30-day all-cause mortality was significantly reduced in the intervention arm, but this difference was not seen at 180 days.[15] Inadequate patient adherence to the telemonitoring intervention or failure to intervene in a timely fashion based on telemonitoring signals may both contribute to the lack of impact of this approach on outcomes in clinical practice.

... enthusiasm has risen for implantable hemodynamic monitoring systems ... which directly estimate cardiac filling pressures, allowing clinicians to intervene earlier and adjust diuretics and other GDMT to avoid decompensation that results in hospitalization.

Recently, enthusiasm has risen for implantable hemodynamic monitoring systems such as the CardioMEMS™ device (St. Jude Medical, St. Paul, MN), which directly estimate cardiac filling pressures, allowing clinicians to intervene earlier and adjust diuretics and other GDMT to avoid decompensation that results in hospitalization. In one study, 500 patients with NYHA class III HF and prior HF hospitalization, irrespective of EF, were randomized to the CardioMEMS device or a control group for at least 6 months. At 6 months, 84 HF-related hospitalizations were reported in the treatment group (n = 270) compared with 120 in the control group (n = 280; rate 0.32 vs 0.44; HR 0.72; 95% CI, 0.60-0.85; P = .0002).[16] Incorporation of such monitoring devices into HF disease management programs may reduce morbidity and unnecessary HF hospitalizations.

State of the Art Pharmacotherapy for Heart Failure With Reduced Ejection Fraction

Pathophysiology of Heart Failure

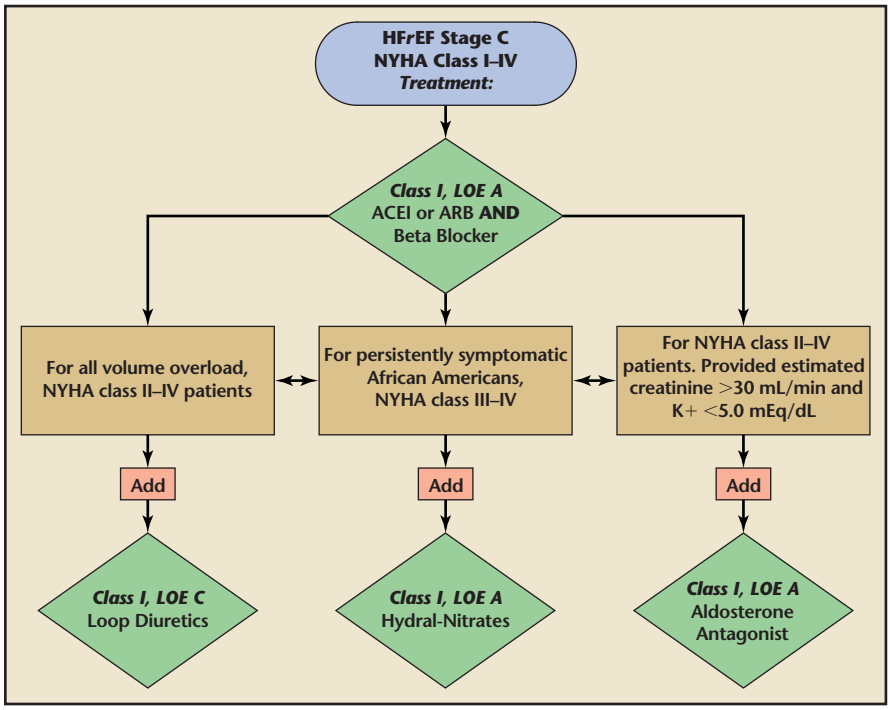
HF in patients with reduced EF is a consequence of sustained neurohormonal activation that is initially adaptive, but then maladaptive, over time. The therapies currently given to patients with HFrEF target the renin-angiotensin-aldosterone system (RAAS) or the sympathetic nervous system, targeting specific hormones such as angiotensin 2, aldosterone, norepinephrine, vasopressin, and endothelin. These hormones are responsible for systemic vasoconstriction, fluid retention, fibrosis, and hypertrophy—all processes that are hallmarks of the progression of the HF syndrome. The balance of this is the effort by the body to counteract the deleterious effects of these neurohormones, including natriuretic peptide systems, nitric oxide, prostaglandins, and bradykinin. Such counterregulatory effects are blunted in most patients with HF.[17]

Guideline-directed Medical Therapies

We begin with discussion of traditional GDMT (Figure 1)[5]; following that we discuss the novel therapies that have recently become part of the GDMT used in the treatment of HFrEF, including neprilysin inhibitors and ivabradine.[18]

Angiotensin-converting Enzyme Inhibitors and Angiotensin Receptor Blockers. Angiotensin-converting enzyme (ACE) inhibitors are one of the cornerstones of therapy for HFrEF. ACE inhibitors

Figure 1. Evidence-based, guideline-directed medical therapy. ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blockers; HFrEF, heart failure with reduced ejection fraction; hydral-nitrates, hydralazine and isosorbide dinitrate; LoE, level of evidence; NYHA, New York Heart Association. Reprinted with permission, *Circulation*. 2013;128:1810-1852. ©2013 American Heart Association, Inc.



have been studied in multiple trials across patients with a broad spectrum of disease, including those with asymptomatic LV dysfunction, those with mild or severe HF symptoms, and those with HF complicating myocardial infarction. All of these studies demonstrate that ACE inhibitors use is associated with reduction in mortality and HF hospitalization. Subsequently, angiotensin receptor blockers (ARBs), which block the action of angiotensin II at the type 1 receptor, were found to be beneficial in most patients with HFrEF. In general, ARBs are most useful in patients intolerant of ACE inhibitors due to cough or angioedema.

As with all HF therapies, it is important to titrate ACE inhibitors or ARBs to target doses achieved in clinical trials or to the maximally tolerated dose in each patient. Several trials have demonstrated that low doses are less effective than higher doses in terms of clinical outcomes such as death or HF hospitalization.[19,20]

β-Blockers. β-blockers (BBs) are the other cornerstone therapy in HF patients. Although initially thought to be deleterious in patients with HF because of negative inotropic effects, the long-term benefits of BBs for improving HF outcomes are unmistakable. The three BBs consistently shown to benefit patients with HFrEF are metoprolol succinate, carvedilol, and bisoprolol. Similar to ACE inhibitors and ARBs, the trials that employed higher doses seem to show greater effects, suggesting that dose titration to target doses is important in achieving the benefits of β-blockade in patients with HFrEF.

Although initially thought to be deleterious in patients with HF because of negative inotropic effects, the long-term benefits of BBs for improving HF outcomes are unmistakable.

Aldosterone Antagonists. Aldosterone antagonists (spironolactone, eplerenone) are the third cornerstone therapy in the treatment of HFrEF. Aldosterone antagonists have been studied in a wide range of patients, including those after myocardial infarction with HF symptoms or LV systolic dysfunction, those with HFrEF and mild HF symptoms (NYHA class II), and those with HFrEF and severe symptoms (NYHA class III-IV). In each of these trials aldosterone antagonism reduced mortality and HF hospitalization. As such, aldosterone antagonists are used in HFrEF patients on ACE inhibitors/ARBs and BBs who remain symptomatic.[5]

Hydralazine, Nitrates, and Digoxin. In patients who remain symptomatic after titration to doses achieved in trials or maximally tolerated doses of ACE inhibitors/ARBs, BBs, and aldosterone antagonists, addition of hydralazine and nitrates or digoxin may be of benefit. Digoxin does not have a mortality benefit, but it reduces HF hospitalizations in patients with HFrEF.[21] Hydralazine and nitrates provide incremental mortality reductions in African American patients with HFrEF who remain symptomatic (NYHA class III-IV) despite ACE inhibitors/ARBs, BBs, and aldosterone antagonists.[5]

Neprilysin as a Therapeutic Target. Neprilysin (also known as neutral endopeptidase) is a zinc-dependent metalloprotease that cleaves and inactivates several vasoactive peptides, including the natriuretic peptides, adrenomedullin, bradykinin, and substance P; as noted, all have important roles in the pathogenesis and progression of HF.[22] Inhibition of neprilysin thus potentiates action of these various vasoactive peptides, leading to exploration of neprilysin inhibition as a therapeutic option for HF. Importantly, because angiotensin II is also a substrate for neprilysin, neprilysin inhibitors must be coadministered with an RAAS blocker.

Previous studies of a neprilysin inhibitor and an ACE inhibitor failed due to unacceptably high rates of angioedema. In a study of patients with HF, omapatrilat, a combination drug of a neprilysin inhibitor and an ACE inhibitor, had no impact compared with enalapril on the primary composite endpoint of death or hospitalization for HF; there were a number of beneficial signals in the secondary endpoints but numerically more cases of angioedema.[23] When a neprilysin inhibitor is used in combination with an ARB there is a lower risk for angioedema. LCZ696, now known as sacubitril/valsartan, a combination angiotensin receptor/neprilysin inhibitor, was studied in the landmark Angiotensin-Neprilysin Inhibitor versus Enalapril in Heart Failure (PARADIGM-HF) trial[24] of patients with HFrEF. The trial began with a sequential run-in period to ensure that every patient randomized could tolerate both enalapril and sacubitril/valsartan target doses. The dose of enalapril (10 mg twice daily) was chosen based on previous HF trials. Ultimately, 8399 patients with

When a neprilysin inhibitor is used in combination with an ARB there is a lower risk for angioedema.

NYHA class II-IV symptoms with an EF ≤ 40% (this entry criterion was modified to ≤ 35% 1 year into the trial), stable on doses of ACE inhibitors/ARBs, and on other background GDMT (BBs and aldosterone antagonists) were validly randomized to receive enalapril versus sacubitril/valsartan. Patients with a history of angioedema, estimated glomerular filtration rate < 30 mL/ min/1.73m^2, symptomatic hypotension, or current decompensated HF were excluded. Most patients enrolled in PARADIGM-HF had NYHA class II-III symptoms.

The investigators of PARADIGM-HF showed that, in patients treated with sacubitril/valsartan in addition to a background of GDMT, there was a 20% reduction in the primary outcome, which was the risk of cardiovascular death or HF hospitalization (HR 0.80; 95% CI, 0.73-0.87; P = .0000002) (Figure 2). With regard to the other endpoints in PARADIGM-HF, there was a 20% reduction in cardiovascular death, a 20% reduction in HF hospitalization, a 16% reduction in overall mortality, a 21% reduction in HF death, and a 20% reduction in sudden death. These effects were apparent early in the trial, with reductions in HF hospitalization apparent during the first 30 days.

With regard to safety endpoints, symptomatic hypotension was more common in the sacubitril/valsartan-treated group. Angioedema was also more frequent in the sacubitril/valsartan-treated group.

Recently, the ACCF/AHA published a focused update to the HF guidelines.[18] Use of sacubitril/valsartan was granted a class I recommendation for patients with chronic HFrEF, stating that patients with NYHA class II-III symptoms who can tolerate an ACE inhibitor or ARB should be changed to an angiotensin receptor neprilysin inhibitor, to further reduce morbidity and mortality (Figure 2).[18] It is important to remember the need for a 36-hour washout period when switching a patient from an ACE inhibitor to sacubitril/valsartan to avoid overlapping of the ACE inhibitor and neprilysin inhibition and the risk of angioedema. A schematic for suggested initiation of sacubitril/valsartan is shown in Table 3. It is recommended that the dose be doubled every 2 to 4 weeks until the target dose and/or maximally tolerated dose is achieved. As with ACE inhibitors and ARBs, it is important to monitor renal function and potassium after initiation and titration of sacubitril/valsartan.

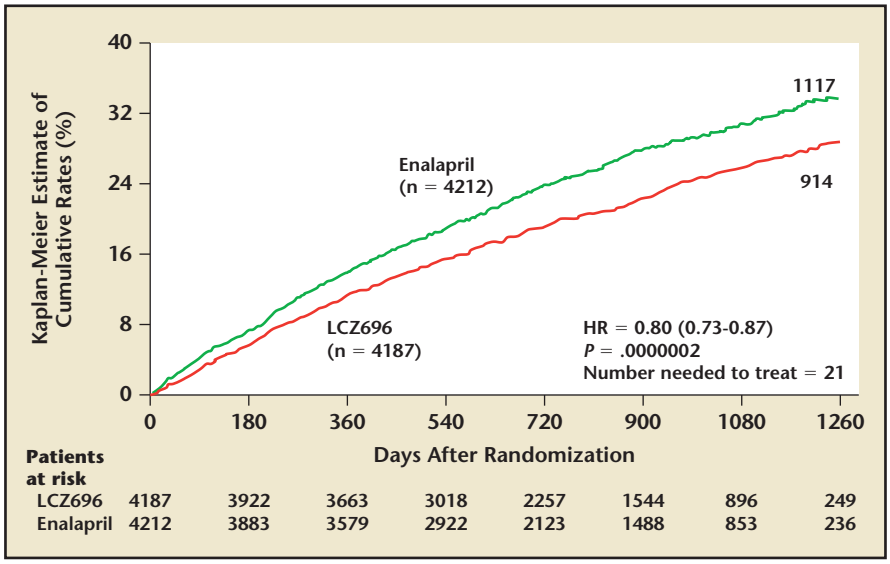


Figure 2. Primary endpoint of the Angiotensin-Neprilysin Inhibitor versus Enalapril in Heart Failure (PARADIGM-HF) trial: cardiovascular death or heart failure hospitalization. HR, hazard ratio. Reprinted with permission from McMurray JJ et al.[24]

Ivabradine. There has been growing recognition of the importance of heart rate control in patients with chronic HF. Recent evidence has revealed heart rate to be an independent predictor of risk in HFrEF and evidence from drug therapy trials suggests that

TABLE 3

Initiation of Sacubitril/Valsartan

Population	Initial Dose
Routine	49/51 mg twice daily
Low-dose ACEI/ARB	24/26 mg twice daily
ACEI/ARB naïve	
eGFR ≤ 30 mL/min/m^2	
Moderate hepatic impairment (Child-Pugh Class B)	
Elderly	

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate.

achievement of HR < 70 beats/min is necessary for improved outcome.[25] As an alternative means to reduce heart rate in those in normal sinus rhythm, the novel agent ivabradine has been explored as a therapy for patients with chronic HFrEF.

Ivabradine is a specific inhibitor of the I_f current involved in sinoatrial nodal activity. Ivabradine reduces the heart rate of patients in normal sinus rhythm without impacting blood pressure. In the Systolic HF Treatment with the I_f Inhibitor Ivabradine Trial (SHIFT) of 6505 subjects with stable chronic, predominantly NYHA class II and III HFrEF, ivabradine therapy added to GDMT resulted in significant improvement in HF hospitalization rates.[26] In terms of safety, patients treated with ivabradine had more bradycardia and atrial fibrillation as well as phosphenes, a visual side effect of rings of light.

In the focused update to the HF guidelines,[18] ivabradine was given a class IIa recommendation highlighting that it might be beneficial to reduce HF hospitalizations in patients with an EF ≤ 35% who are already receiving GDMT (including BBs at the maximally tolerated dose), and in those who are in sinus rhythm with a heart rate > 70 beats/min at rest. As such, it is recommended to increase BB dose to the target or maximally tolerated dose; if the patient's resting heart rate remains ≥ 70 beats/min, it is recommended to consider adding ivabradine.

Game-changing Devices for Heart Failure: Electricity and Catheter-based Therapies

As HF progresses, there are histopathologic changes that occur, including cardiomyocyte hypertrophy, extracellular fibrosis, and myocyte necrosis and apoptosis. Additionally, changes occur at the electrical level and affect the sinus node, the atrioventricular node, bundle branches, and the Purkinje network. Ultimately, this results in prolonged interventricular and intraventricular conduction, which, in turn, causes regional mechanical delay. Such delays may result in reduced systolic function, functional mitral regurgitation, and LV dilation and adverse remodeling. Additionally, the accompanying prolonged QRS may lead to loss of homogenous segmental LV contraction, also known as electromechanical or mechanical dyssynchrony. QRS duration and dyssynchrony have been identified as predictors of worsening HF, sudden cardiac death, and total death.[27] Table 4 provides a list of these devices.

Cardiac Resynchronization

Biventricular pacing or cardiac resynchronization therapy (CRT) is a therapy in which three leads are implanted into the heart; one lead is placed in the right atrium, the second lead is placed in the right ventricle, and the third lead–the left ventricle lead–is placed in the coronary sinus. CRT can improve ventricular systolic function and reduce mitral regurgitation, and is an effective mediator of reverse remodeling with reduction in chamber dimensions. In addition to structural improvements, functional improvement has been demonstrated for exercise capacity and reduction of HF symptoms on

TABLE 4

New Devices for Heart Failure Management

Cardiac resynchronization and pacing
Triangular pacing
Quadrangular pacing
Multipoint pacing
Left ventricular endocardial pacing
WiSE technology[a]
Neuromodulation therapies
Vagal nerve stimulation
Carotid baroreceptor stimulation
Spinal cord stimulation
Renal denervation
Phrenic nerve pacing
Remote monitoring
CRT-D sensors
Catheter-based therapies
MitralClip[b]
Parachute device[c]
Biopolymers injection
Stem cell catheter delivery

CRT-D, chronic resynchronization therapy-defibrillator.
[a]WiSE Wireless Technology (EBR Systems, Sunnyvale, CA).
[b]MitraClip (Abbott Laboratories, Lake Bluff, IL).
[c]Parachute device (CardioKinetix, Menlo Park, CA).

the Minnesota Living with Heart Failure scale.[28]

There is a plethora of data suggesting CRT improves outcomes in patients with NYHA class III and IV HF. One such study is the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial that enrolled 1520 patients with NYHA class III or IV HF and a QRS duration of at least 120 ms. GDMT was compared with CRT pacing therapy without backup defibrillation (CRT-P) and to CRT therapy with defibrillation backup (CRT-D). Both CRT-P and CRT-D reduced the risk of the primary composite endpoint of time to death from or hospitalization for any cause by approximately 20% as compared with GDMT alone. CRT-D reduced the mortality rate by 36% compared with medical therapy.[29] The Cardiac Resynchronization in Heart Failure (CARE-HF) trial enrolled patients with NYHA class III or IV HF and a QRS duration >150 ms or QRS duration 120 to 150 ms with echocardiographic evidence of dyssynchrony to receive GDMT versus GDMT with CRT-P. There was a 36% reduction in the death rate in the CRT-P group,[30] illustrating the benefit of CRT-P without defibrillator backup.

CRT is also beneficial for patients with NYHA class I and II HF. The Cardiac-Resynchronization Therapy for Mild-to-Moderate Heart Failure (RAFT) study enrolled patients with NYHA class II and III HF, an EF of ≤ 30%, and a QRS of at least 120 ms (or 200 ms if paced) to receive an implantable cardioverter-defibrillator alone or CRT-D. In subgroup analysis of the patients with NYHA class II HF, there was a 27% reduction in the primary endpoint of death or hospitalization for HF in the CRT-D group (HR 0.73; 95% CI, 0.61-0.88; $P = .001$).[31] Similarly, in the Cardiac-Resynchronization Therapy for the Prevention of Heart-Failure Events (MADIT-CRT) trial, patients with NYHA class I or II HF and a QRS duration of at least 130 ms who received CRT-D had decreased risk of HF events.[32]

It is important to remember that not all patients respond to CRT. Using metrics such as QoL or improved NYHA class, approximately 30% of patients are nonresponders. Conversely, when using remodeling endpoints, 40% to 50% of patients are nonresponders.[33] The three primary determinants of nonresponsiveness are patient selection, LV lead placement, and optimal programming and follow-up. There may be ways to optimize patient selection, including using echocardiography to identify parameters such as mechanical dyssynchrony to identify which patients will do well. Additional imaging modalities such as magnetic resonance imaging and computed tomography can further delineate extent of mechanical dyssynchrony, coronary venous anatomy, and presence or absence of scar. Three-dimensional echocardiography can be used to reconstruct an image of the heart with the coronary venous anatomy, and using integrative strategies to determine the most mechanically delayed area of the heart in order to place the LV lead there.

More novel pacing modalities exist that may improve response. Triangular pacing, in which an additional lead is placed on the right ventricle outflow tract, another lead in the right ventricle apex, and a third lead on the epicardial surface, has been explored as a way to recruit more myocardium.[34] There is also a novel concept of quadrangular pacing, in which a fourth lead is placed to recruit even more myocardium in dilated hearts. Quadripolar leads have four electrodes along the lead that can be used to pace the heart and, as such, reduce scarring due to the different pacing points. Quadripolar leads also allow positioning away from the phrenic nerve, reduce periprocedural complications, and have been shown to improve long-term outcomes.[35] Multipoint pacing is another new concept that involves sequential pacing from two electrodes and can enhance reverse remodeling. There are large randomized studies underway to study this pacing modality.

There have also been newer strategies aimed at pacing the LV endocardium in the area most electrically delayed. A recent study showed that transvenous LV endocardial pacing can be done safely, and 6-month follow-up data showed improvement in NYHA class and a reduction in LV end-systolic volumes.[36] The impact on long-term outcome is still unknown, but this pacing strategy may be used in the near future. Another evolving pacing modality is the WiSE Wireless Technology (EBR Systems, Sunnyvale, CA), which allows for synchronized, targeted LV pacing. A phased array ultrasound transmitter is implanted in the intercostal space and a receiver electrode is retrogradely, transaortically implanted in the LV endocardial lead. The array transmitter transmits ultrasound energy, which is converted to electrical pulse, and can then pace the heart. It is a leadless system in the LV that is paced

A recent study showed that transvenous LV endocardial pacing can be done safely, and 6-month follow-up data showed improvement in NYHA class and a reduction in LV end-systolic volumes.

by an ultrasound transmitter on the surface of the chest. This system was evaluated in a small cohort of patients and shown to be useful in patients who were nonresponders to resynchronization therapy.[37] Primary and secondary endpoint data were available for 15 of the 19 patients, and 6-month data were available for 8 patients. At 1 month, all 15 patients demonstrated biventricular pacing on 12-lead electrocardiogram. The QRS interval narrowed by 46 ms at 1 month and by 23 ms at 6 months. NYHA class also significantly improved between baseline and 6 months. All patients showed improvements on their clinical composite score. It was also shown to be useful in patients in whom CRT could not be performed because of challenging coronary venous anatomy. Larger studies using this technology are underway.

Emerging Neuromodulation Therapies

These strategies modulate the autonomic nervous system and work to shift the sympathovagal balance. This can help in cardiovascular remodeling and, as such, improved outcomes for patients with HF.

Vagal Nerve Stimulation

In vagal nerve stimulation a lead is implanted around the vagus nerve and tunneled down to a nerve stimulator on the right side of the chest wall; this is then connected to the heart through a right ventricular lead. Vagal nerve stimulation has been studied for improvement of cardiac function and symptoms, and as an antiarrhythmic strategy. Any benefit of this therapy may be a consequence of multiple mechanisms, including heart-rate lowering, blunting of the sympathetic axis, and inhibition or down-regulation of the RAAS.[38] Further studies are needed on this modality, as studies have produced mixed results.

Carotid Baroreceptor Stimulation

A proof-of-concept study showed that carotid baroreceptor stimulation improved muscle sympathetic nerve activity and clinical measures of QoL and functional capacity in patients with NYHA class III HF and an EF $<$ 40%. There was a 30% reduction in sympathetic activity and 85% reduction in hospitalizations.[39] The recently published Baroreflex Activation Therapy for the Treatment of Heart Failure With a Reduced Ejection Fraction (BAROSTIM HF) looked at patients with an EF $\leq$ 35% and NYHA class III symptoms on GDMT; it found that carotid baroreceptor stimulation improved the distance walked in 6 minutes (59.6 $\pm$ 14 m vs 1.5 $\pm$ 13.2 m; $P = .004$), QoL score (-17.4 ± 2.8 points vs 2.1 ± 3.1 points; $P < .001$), and NYHA functional class ranking ($P = .002$ for change in distribution).[40] There are larger randomized controlled studies that are currently underway.

Spinal Cord Stimulation

Spinal cord stimulation is a strategy that has been used for treatment of refractory angina. It was later found that stimulation of the T4/T3 area in animals can also shift the sympathovagal balance and favorably remodel the heart. Subsequently, a study done in humans did not provide evidence to support a meaningful change in outcomes for HF patients receiving spinal cord stimulation. The change in LV end-systolic volume index was not different between the study randomization arms at 6 months (-2.2 [95% CI, -9.1-4.6] vs 2.1 [95% CI, -2.7-6.9]; $P = .30$).[41] This is also an area that needs further study.

Renal Denervation

Renal denervation involves the delivery of low-energy radiofrequency ablation to the renal artery. It has been studied extensively in refractory hypertension and studies have come with mixed results. Renal denervation reduces sympathetic nervous system activity, restores impaired natriuresis, reduces filling pressures, and reverse-remodels the heart. There are studies suggesting that it may also reduce LV hypertrophy; as such, it may play a role in diastolic HF.[38] There are current trials underway to test this therapy in HF.

Phrenic Nerve Pacing

This modality has been used in pilot studies in patients with sleep apnea. Through pacing the phrenic nerve in patients who are predisposed to central sleep apnea, there was a 55% reduction in the apnea/hypopnea index from baseline to 3 months (49.5 $\pm$ 14.6 episodes/h vs 22.4 $\pm$ 13.6 episodes/h of sleep; 95% CI for change, -32.3 to -21.9; $P < .0001$). There was significant improvement in the central apnea index, oxygenation, and arousal.[42] This may be of benefit in patients with HF in whom sleep apnea is common. Again, further studies are needed to evaluate the long-term efficacy of such a device.

Through pacing the phrenic nerve in patients who are predisposed to central sleep apnea, there was a 55% reduction in the apnea/hypopnea index from baseline to 3 months…

Remote Monitoring

Home telemonitoring in patients with HF has come with mixed

results, and it may be a matter of selecting appropriate patients for this monitoring strategy. There are multiple sensors in CRT-D devices used in patients with HF that can provide information on heart sounds, thoracic impedance, respiration, and physical activity. One study demonstrated that monthly review of these devices can predict HF hospitalizations within the subsequent month. Patients with a positive combined HF device diagnostics had a 5.5-fold increased risk of HF hospitalization with pulmonary signs or symptoms within the next month (HR 5.5; 95% CI, 3.4-8.8; $P < .0001$), and the risk remained high after adjusting for clinical variables (HR 4.8; 95% CI, 2.9-8.1; $P < .0001$).[43] Future work in this area involves using the data from these sensors for early intervention and possible reduction of HF hospitalizations and readmissions.

Catheter-based Therapies

There are many novel catheter approaches for the treatment of HF; most are experimental and many have provided only preliminary information. Many of these devices need further studies to evaluate their use in HF. In a small study of CRT nonresponders with functional mitral regurgitation the MitraClip (Abbott Laboratories, Lake Bluff, IL) improved functional class, increased LVEF, and reduced ventricular volume in approximately 70% of the patients in this study.[44] Another device is the Parachute device (CardioKinetix, Menlo Park, CA) in patients with HF and a LV aneurysm. The device reduces end-diastolic pressure and wall stress and improves LV geometry. Studies are needed to measure long-term outcomes with this device.

Another catheter-based strategy involves the injection of biopolymers into the walls of the heart; these polymers alter the remodeling of the heart, reduce LV wall stress, and may prevent further dilatation and negative remodeling.[45] Again, this is an investigational strategy whose impact on long-term outcome remains to be seen. Stem cell catheter delivery in CRT nonresponders is another investigational strategy. There are multiple ongoing studies looking at stem cell transplantation in both ischemic and nonischemic cardiomyopathy.

Conclusions

HF is a chronic and complex disease entity. Many of the therapies used for HF were developed decades ago but remain ingrained in the guidelines for its management. There are new strategies for monitoring and treatment of HF. It is important to pay attention to these novel approaches and apply them to the subset of patients who may show benefit in order to improve morbidity and mortality in our HF patients. ■

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MAIN POINTS

- Risk stratification is an important component of the evaluation of patients with heart failure (HF). It is important to communicate prognostic information to patients in an effort to motivate them to be vigilant of their symptoms and to improve adherence to guideline-directed medical therapies (GDMT) and lifestyle recommendations. It is also important for clinicians, as it assists them in managing frequency of follow-up and referral for advanced therapies such as transplantation or mechanical circulatory support.
- Recently, enthusiasm has risen for implantable hemodynamic monitoring systems that directly estimate cardiac filling pressures, allowing clinicians to intervene earlier and adjust diuretics and other GDMT to avoid decompensation that results in hospitalization.
- Angiotensin-converting enzyme (ACE) inhibitors are one of the cornerstones of therapy for HF with reduced ejection fraction (HFrEF). Angiotensin receptor blockers (ARBs), which block the action of angiotensin II at the type 1 receptor, are beneficial in most patients with HFrEF. ARBs are most useful in patients intolerant of ACE inhibitors due to cough or angioedema. As with all HF therapies, it is important to titrate ACE inhibitors or ARBs to target doses achieved in clinical trials or to the maximally tolerated dose in each patient in order to provide the most benefit to the patients.
- Recently, the American College of Cardiology Foundation and the American Heart Association published a focused update to the HF guidelines. Use of sacubitril/valsartan was granted a class I recommendation for patients with chronic HFrEF, stating that patients with New York Heart Association class II-III symptoms who can tolerate an ACE inhibitor or ARB should be changed to an angiotensin receptor neprilysin inhibitor, to further reduce morbidity and mortality.
- Cardiac resynchronization therapy can improve ventricular systolic function and reduce mitral regurgitation, and is an effective mediator of reverse remodeling with reduction in chamber dimensions.
- Emerging neuromodulation therapies such as vagal nerve stimulation, carotid baroreceptor stimulation, spinal cord stimulation, and renal denervation modulate the autonomic nervous system and work to shift the sympathovagal balance, which helps in cardiovascular remodeling and, as such, improved outcomes for patients with HF. Many of these therapies are currently experimental but have shown promise.

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Evaluation Form

Advances in Heart Failure Management: Improving Outcomes With Innovation

Activity ID: 11763

Please complete the following evaluation questions to receive your certificate.

1. **What degree best describes you?**

○ MD/DO ○ PA/PA-C ○ NP ○ RN
○ PharmD/RPh ○ PhD ○ Other, please specify:

2. **What is your area of specialization?**

○ Cardiology, General ○ Cardiology, Interventional ○ Cardiology, Echocardiography
○ Cardiology, Electrophysiology ○ Internal Medicine ○ Preventive Medicine
○ Family Medicine ○ Other, please specify:

3. **Which of the following best describes your *primary* practice setting?**

○ Solo Practice ○ Group Practice ○ Government
○ University/teaching system ○ Community Hospital ○ HMO/managed care
○ Non-profit/community ○ I do not actively practice ○ Other, please specify:

4. **How long have you been in practice?**

○ More than 20 years ○ 11-20 years ○ 6-10 years
○ 1-5 years ○ Less than 1 year ○ I do not directly provide care

5. **Approximately how many patients do you see each week?**

○ Less than 50 ○ 50-99 ○ 100-149
○ 150-199 ○ 200+ ○ I do not directly provide care

6. **How many patients with heart failure do you currently see each week?**

○ Less than 5 ○ 5-15 ○ 16-25 ○ 26-35
○ 36-45 ○ 46-55 ○ 56 or more ○ I do not directly provide care

7. **Please select the extent to which you agree/disagree that the activity supported the achievement of each learning objective.**

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
Implement heart failure classification systems, such as the ACC/AHA stages or NYHA functional classification, in order to effectively stage patients and direct treatment goals	⑤	④	③	②	①
Evaluate the role of biomarkers as prognostic indicators, and to monitor therapy for patients with reduced or preserved ejection fraction heart failure	⑤	④	③	②	①
Implement pivotal study data for recently approved therapies for patients with heart failure	⑤	④	③	②	①
Implement electricity and catheter-based therapies for heart failure patients who are appropriate candidates	⑤	④	③	②	①

8. Please select the extent to which you agree/disagree that the activity achieved the following:

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
The faculty were effective in presenting the material	⑤	④	③	②	①
The content was evidence based	⑤	④	③	②	①
The educational material provided useful information for my practice	⑤	④	③	②	①
The activity enhanced my current knowledge base	⑤	④	③	②	①
The activity provided appropriate and effective opportunities for active learning (e.g., case studies, discussion, Q&A, etc.)	⑤	④	③	②	①
The opportunities provided to assess my own learning were appropriate (e.g., questions before, during or after the activity)	⑤	④	③	②	①

9. Based upon your participation in this activity, do you intend to change your practice behavior? (choose only one of the following options)

- ○ I do plan to implement changes in my practice based on the information presented
- ○ My current practice has been reinforced by the information presented
- ○ I need more information before I will change my practice

10. Thinking about how your participation in this activity will influence your patient care, how many of your patients are likely to benefit?

Please use a number (example 250):

11. If you plan to change your practice behavior, what type of changes do you plan to implement? (check all that apply)

- ○ Apply latest guidelines
- ○ Change in pharmaceutical therapy
- ○ Change in non-pharmaceutical therapy
- ○ Change in diagnostic testing
- ○ Choice of treatment/management approach
- ○ Change in current practice for referral
- ○ Change in differential diagnosis
- ○ Other, please specify:

12. How confident are you that you will be able to make your intended changes?

○ Very confident ○ Somewhat confident ○ Unsure ○ Not very confident

13. Which of the following do you anticipate will be the primary barrier to implementing these changes?

- ○ Formulary restrictions
- ○ Time constraints
- ○ System constraints
- ○ Patient adherence/compliance
- ○ Insurance/financial issues
- ○ Lack of multidisciplinary support
- ○ Treatment related adverse events
- ○ Other, please specify:

14. Was the content of this activity fair, balanced, objective and free of bias?

○ Yes ○ No, please explain:

15. Please list any clinical issues/problems within your scope of practice you would like to see addressed in future educational activities:

SELF-ASSESSMENT POST-TEST

Advances in Heart Failure Management: Improving Outcomes With Innovation

In order to receive credit, participants must complete the evaluation and post-test electronically by visiting www.cmeuniversity.com.

1. A 44-year-old woman with idiopathic dilated cardiomyopathy and an ejection fraction of 33% presents for follow-up. She says she has been feeling better but still gets short of breath when she climbs the single flight of stairs to her apartment. Her vital signs today include a resting heart rate of 67 beats per minute and a blood pressure of 110/72 mm Hg. Results of her physical examination are unremarkable. Her medications include carvedilol, 25 mg twice daily, lisinopril, 20 mg daily, spironolactone, 25 mg daily, and furosemide, 20 mg daily. Her laboratory test results are unremarkable.

Which of the following is the next best step in her management?

a. Increase lisinopril to 40 mg daily
b. Increase furosemide to 40 mg daily
c. Switch to sacubitril/valsartan 49/51 mg twice daily
d. Make no medication changes at this time

2. A 51-year-old man with ischemic cardiomyopathy and an ejection fraction of 29% presents for follow-up. He is able to walk up to two blocks without getting short of breath. His vital signs today include a resting heart rate of 87 beats per minute and a blood pressure of 118/68 mm Hg. Results of his physical examination are unremarkable. His medications include metoprolol succinate, 200 mg twice daily, sacubitril/valsartan, 97/103 mg twice daily, eplerenone, 50 mg daily, and furosemide, 40 mg daily. His laboratory test results are unremarkable.

Which of the following is the next best step in his management?

a. Add carvedilol, 12.5 mg twice daily
b. Add ivabradine, 5 mg twice daily
c. Switch from metoprolol succinate to carvedilol for better heart rate control
d. Add digoxin

3. Ivabradine is indicated in a patient with nonischemic cardiomyopathy, an ejection fraction of 35%, New York Heart Association class II heart failure, and atrial fibrillation with an uncontrolled ventricular response ranging from 120 to 130 beats per minute at rest on a maximum dose of a β-blocker and digoxin.

a. True
b. False

4. A 34-year-old man with idiopathic dilated cardiomyopathy and an ejection fraction of 29% presents for follow-up. He has New York Heart Association class II heart failure symptoms. His vital signs today include a resting heart rate of 87 beats per minute and a blood pressure of 128/74 mm Hg. Results of his physical examination are unremarkable. His medications include carvedilol, 12.5 mg twice daily, lisinopril, 20 mg daily, eplerenone, 50 mg daily, and furosemide, 20 mg as needed. His laboratory tests results are unremarkable.

Which of the following is the next best step in his management?

a. Add ivabradine, 5 mg twice daily
b. Change furosemide to scheduled daily dosing
c. Increase carvedilol to 25 mg twice daily
d. Make no changes today

5. In the landmark Angiotensin-Neprilysin Inhibitor versus Enalapril in Heart Failure (PARADIGM-HF) trial which of the following was true?

a. There was a reduction in the risk of cardiovascular death but there was no reduction in heart failure hospitalization
b. The majority of patients had New York Heart Association class IV symptoms
c. It found benefit for the use of sacubitril/valsartan in patients with heart failure with preserved ejection fraction
d. There was a 20% reduction in the primary outcome, which was the risk of cardiovascular death or heart failure hospitalization