Heart failure affects more than 23 million people worldwide.1 In the United States, more than 5.8 million patients have heart failure and more than 550,000 patients are diagnosed each year.1 Heart failure accounts for close to 1 million hospitalizations a year with 25% of those patients readmitted to a hospital within 30 days.1 Heart failure consists of a wide spectrum of abnormalities, ranging from heart failure with preserved ejection fraction to heart failure with reduced ejection fraction (defined as a left ventricular [LV] ejection fraction of 40% or less).2

Guidelines published in 2013 by the American College of Cardiology Foundation/American Heart Association (ACC/AHA) helped to expand the use of evidence-based pharmacotherapies, reducing the rate of sudden death in patients with heart failure by 44%.3 In 2016, the AHA/ACC/Heart Failure Society of America (HFSA) released a joint focused guideline update for heart failure management specifically related to two new medications recommended to further reduce hospitalizations and increase life expectancy in patients with heart failure. These innovative therapies can significantly improve patients’ quality of life and reduce the healthcare costs associated with managing heart failure.

**Keywords:** heart failure, ivabradine, angiotensin receptor-neprilysin inhibitor, ARNI, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker
PATHOPHYSIOLOGY
Heart failure is defined as the heart’s inability to supply sufficient blood to meet the body’s metabolic requirements. Cardiac injury or dysfunction that precipitates cardiac remodeling can result in heart failure. Common causes of injury or dysfunction include ischemic heart disease, chronic hypertension, and valvular disorders. Other contributing factors include congenital heart defects, diabetes, anemia, and alcohol abuse. Early compensatory mechanisms become active when decreased cardiac output stimulates baroreceptors and the sympathetic nervous system. As a result of low cardiac output, decreased renal perfusion activates the renin-angiotensin-aldosterone system, which attempts to restore cardiac output and tissue perfusion. During times of volume overload in the ventricles, the myocardium secretes natriuretic peptides. These neurohormonal responses of volume overload in the ventricles, the myocardium secretes natriuretic peptides. Two biomarkers—brain natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP)—are secreted during heart failure exacerbations, decreasing with treatment. If these values do not fall after aggressive heart failure therapy, the patient is at significant risk of death or hospitalization. Levels of these biomarkers are measured in the blood and are elevated during acute heart failure exacerbations, decreasing with treatment. If these values do not fall after aggressive heart failure therapy, the patient is at significant risk of death or hospitalization.

SIGNS AND SYMPTOMS
The primary symptoms of acute decompensated heart failure are exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and fatigue. Common clinical signs of fluid retention include bibasilar crackles, pleural effusions, tachycardia, S₃ gallop, jugular venous distension, ascites, hepatomegaly, and pitting edema. Patients with chronic heart failure who have been medically optimized may present in acute decompensated heart failure without signs or symptoms of fluid overload. Many patients treated for an acute decompensation of heart failure will experience a recurrence of fluid accumulation, promoting another cycle of decompensation and requiring repeat hospitalizations.

DIAGNOSTIC STRATEGIES
Heart failure is a complex clinical syndrome and the diagnosis is made clinically through a careful history and physical examination. Both the ACC/AHA stages of heart failure and the New York Heart Association (NYHA) functional classification provide useful and complementary information about the presence and severity of heart failure. The ACC/AHA stages emphasize the disease development and progression and can be used to describe patients and populations; the NYHA classes focus on exercise capacity and the symptomatic status of the disease. These stages and functional classifications guide clinical judgment in treating patients with or at risk for heart failure.

The 2013 guideline recommended that the initial evaluation of patients presenting with signs and symptoms of acute decompensation of previously undiagnosed heart failure include a complete blood cell count, urinalysis, serum electrolytes (including calcium and magnesium), blood urea nitrogen, serum creatinine, glucose, fasting lipid profile, liver function tests, and thyroid-stimulating hormone. Identifying and managing comorbidities can significantly improve outcomes for patients with heart failure. The 2013 guideline also recommended obtaining an anterior-posterior chest radiograph in patients with heart failure or at risk for it, to look for cardiomegaly, pulmonary congestion, and other possible causes of their symptoms. However, considering the low sensitivity and specificity of the chest radiograph, it should not be the sole determinant of the diagnosis of heart failure.

Obtain biomarker levels The 2013 guideline recommended two biomarkers—brain natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP)—to help diagnose heart failure. The 2017 update reemphasizes the usefulness of these biomarkers for diagnosing and evaluating acute decompensated and chronic heart failure and for differentiating pulmonary from cardiac causes in patients with shortness of breath. According to the 2017 update, an accurate prognosis of acute decompensated heart failure is best made by obtaining baseline levels of natriuretic peptide biomarkers when the patient is admitted to the hospital. Levels of these biomarkers are measured in the blood and are elevated during heart failure exacerbations, decreasing with treatment. If these values do not fall after aggressive heart failure therapy, the patient is at significant risk of death or hospitalization.

Learning objectives
- Describe the changes made to the 2013 ACCF/AHA heart failure guidelines with the 2016 and 2017 updates.
- Explain the benefits of non-pharmacologic therapy for heart failure.
- Compare and contrast the use of ACE inhibitors or ARBs with an angiotensin receptor neprilysin inhibitor and the use of beta-blockers with ivabradine.

Key points
- Heart failure is a leading cause of hospital admissions and death.
- A guideline update recommends replacing an ACE inhibitor or ARB with an ARNI for patients with stage C heart failure with reduced ejection fraction.
- These patients also may be helped by ivabradine, which lowers heart rate without reducing BP.
New data suggest that natriuretic peptide biomarker screening and early intervention by a cardiovascular specialist to optimize direct medical therapy may prevent LV dysfunction or new-onset heart failure.1 However, consistent evidence for improvement in mortality and cardiovascular outcomes is lacking. The 2017 update does not provide recommendations related to natriuretic peptide-guided therapy or serial measurements of BNP or proBNP levels for the purpose of reducing hospitalizations or deaths.5

Cardiac troponin I and T, cardiac biomarkers that indicate cardiac muscle damage in patients with acute coronary syndrome, are found at abnormal levels in patients with heart failure.2 The 2016 guideline recommended measuring these biomarkers in patients presenting with acute decompensation of heart failure.3 Elevated troponin levels in patients with acute decompensated or chronic ambulatory heart failure are associated with a worse clinical outcome and increased mortality; decreasing levels over time indicate a better prognosis.2

**Perform a noninvasive cardiac evaluation** The guideline recommends asking patients about any history of palpitations or dysrhythmias and obtaining a 12-lead electrocardiogram.2 A 24-hour ambulatory electrocardiography device or event recorder may be useful to evaluate rate control and the type of dysrhythmia.2 The 2013 guideline recommends two-dimensional echocardiography as the most useful diagnostic test for evaluating patients with or at risk for heart failure. Transthoracic or transesophageal echocardiogram in patients with suspected heart failure can help identify disease and lead to appropriate medical care.2

**Perform an invasive cardiac evaluation** Right-heart catheterization, also known as pulmonary artery catheterization, is a more invasive technique used to evaluate and manage advanced heart failure. The 2013 guideline recommended right-heart catheterization for patients with a clinically indeterminate volume status, those in respiratory distress, or those who do not respond to initial therapy for heart failure.2 A catheter is advanced from the femoral or internal jugular vein through the right side of the heart and into the pulmonary artery to assess intracardiac filling pressures, quantify LV ejection fraction, and monitor the patient’s hemodynamic response to medical therapies. Routine use of right-heart catheterization is not recommended in normotensive patients with acute decompensated heart failure.2

**HISTORICAL PERSPECTIVE**

Treatment of heart failure has evolved over the past 20 years, with the focus shifting from controlling symptoms to reversing the cardiac dysfunction and remodeling that occurs. Terminology has changed with the improved understanding of the disease process. The condition was once commonly referred to as congestive heart failure but the preferred term today is heart failure. This term encompasses all patients, including those with a primary filling defect (diastolic heart failure), who may not present with symptoms of pulmonary congestion and have a preserved, or normal, ejection fraction. Patients with a normal ejection fraction account for almost 50% of patients with heart failure.2 Describing heart failure as left-sided, right-sided, systolic, diastolic, acute, or chronic remains useful in understanding its pathophysiology and current status.

**NONPHARMACOLOGIC MANAGEMENT**

The nonpharmacologic management of patients with heart failure consists of a multifaceted approach. According to the 2013 guideline, patient education, sodium intake restriction, exercise training, and cardiac rehabilitation all can be used to improve patient outcomes.2 The 2017 update recommends continuous positive airway pressure (CPAP) for patients with heart failure and obstructive sleep apnea (OSA), and recommends against adaptive servo-ventilation for patients with heart failure and central sleep apnea.2 Appropriate use of these interventions yields many benefits, including a reduction in symptoms, an improved quality of life, reduced hospitalizations, and reduced mortality.

**Patient education** Patients with heart failure must receive specific education about self-care.2 Emphasize the importance of taking medications as prescribed, remaining physically active, and taking their weight each morning. Teach patients to identify signs of fluid retention and how to adjust their diuretic therapy or contributing dietary factors as needed. Establish a diuretic strategy that patients can implement as needed and encourage patients to communicate with their healthcare providers about any changes in their volume status and daily diuretic dosage. Advise patients to restrict alcohol consumption and avoid tobacco; provide support for cessation if necessary. Patients with heart failure should avoid nonsteroidal anti-inflammatories or use them with caution.2

Remind patients to speak with their healthcare provider before starting any new medications. Patient education and adherence can help reduce healthcare costs, hospitalizations, and patient mortality.2

**Restricting sodium intake** Patients with symptomatic heart failure should restrict their sodium intake to reduce congestive symptoms. Giving precise recommendations about daily sodium intake is challenging because heart failure and comorbidities have variable effects on sodium homeostasis.2 To minimize the development of hypertension, LV hypertrophy, and cardiovascular disease, the AHA recommends a maximum sodium intake of 1.5 g per day for most patients with AHA stage A or B heart failure.2 Data are insufficient to endorse any specific level of sodium intake for patients with stage C or D heart failure. Clinicians are encouraged to consider restricting sodium intake to less than 3 g per day for patients with stage C or D heart failure, to reduce heart failure exacerbation, as the typical sodium intake is more than 4 g per day in the general population.2
Exercise training and cardiac rehabilitation Exercise is safe and effective for patients with heart failure who can participate. Cardiac rehabilitation can be useful in clinically stable patients with heart failure. Regular physical activity and cardiac rehabilitation have numerous benefits, including improvement of functional capacity, improved quality of life, and reduced mortality.

OSA vs. central sleep apnea Because patient response to therapy for OSA and central sleep apnea differs, distinguishing these two conditions in patients with heart failure is crucial. Nocturnal CPAP can improve sleep quality and reduce daytime sleepiness in patients with OSA. However, CPAP has shown no benefit in cardiovascular events for patients with heart failure and OSA.

The 2017 update recommends against using adaptive servo-ventilation in patients with heart failure and central sleep apnea. A recent study found that these patients had higher mortality when this type of ventilation was used. A decision to refer a patient for a sleep study should be based on clinical judgment.

PHARMACOLOGIC MANAGEMENT
The 2013 guideline outlined optimal medications, as defined by the term guideline-directed medical therapy, for patients with stage C heart failure with reduced ejection fraction. This therapy consists of angiotensin-converting enzyme (ACE) inhibitors (or angiotensin receptor blockers [ARBs] for patients who cannot tolerate ACE inhibitors), and one of three beta-blockers (bisoprolol, carvedilol, or metoprolol succinate).

Additional therapy for certain patients may include loop diuretics, aldosterone receptor antagonists, anticoagulants, digoxin, and combination hydralazine/isosorbide dinitrate.

UPDATED GUIDELINES
The 2017 update discusses new pharmacologic therapies for patients with stage C heart failure with reduced ejection fraction: an angiotensin receptor-neprilysin inhibitor (ARNI) and a sinoatrial node modulator. The update was proceeded by two important studies that have led to a global change in pharmacologic treatment guidelines for heart failure. Implementing these therapies has been shown to reduce heart failure–related hospitalizations and reduce cardiovascular and all-cause mortality.

ARNI In the Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor with ACE inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial, the ARNI (a combination of sacubitril and valsartan) demonstrated its superiority in reducing mortality and morbidity risk compared with the gold standard, the ACE inhibitor enalapril. Patients taking the ARNI had a 20% reduction in cardiovascular mortality and reduced hospitalizations for heart failure over 27 months compared with patients receiving a target dose of 10 mg enalapril twice daily. Using data from the PARADIGM-HF trial, researchers estimated that patients treated with an ARNI instead of an ACE inhibitor or ARB would gain an additional 1 to 2 years of life and have a significant reduction in hospitalizations.

Neprilysin is a neutral endopeptidase that is elevated in patients with heart failure. Primarily found in the kidney, it can exist in numerous tissues, including the vascular smooth muscle, lung, and cardiac myocytes. Neprilysin breaks down and inactivates many peptides that have vasodilatory and other favorable cardiovascular effects, such as the atrial and B-type natriuretic peptides, bradykinin, and adrenomedullin. However, neprilysin also has favorable cardiovascular effects: it can inactivate systemic vasoconstrictors such as endothelin I and angiotensin II. Because sacubitril for neprilysin inhibition alone would have mixed effects in managing patients with heart failure with reduced ejection fraction, it has been combined with the ARB valsartan to minimize the undesirable effects of angiotensin II.

One of the first studies to demonstrate the potential benefit of neprilysin inhibition for patients with heart failure was the IMPRESS randomized trial, which compared vasopeptidase inhibitor, omapatrilat, and lisinopril on exercise tolerance and morbidity in patients with heart failure. Omapatrilat is a dual inhibitor of ACE and neprilysin. In the IMPRESS trial, omapatrilat showed a greater reduction in risk of death or hospitalization for heart failure than enalapril alone; however, the effect was based on a small number of clinical events observed in patients who were treated for 6 months.

Subsequently, the Omapatril Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERture) study was performed to definitively compare the effects of omapatrilat and enalapril on outcomes in patients with heart failure. The study determined that omapatrilat reduced morbidity and mortality of patients with moderate to severe heart failure compared with enalapril alone. The OVERture trial was ended because of an associated increased risk of angioedema. This study confirmed the potential value of neprilysin inhibition in addition to RAAS modulation for patients with heart failure, and ultimately resulted in the development of the ARNI.

Patients with chronic heart failure (NYHA classes II through IV), an elevated plasma BNP or NT-proBNP level, and an LV ejection fraction less than 40% should be considered for treatment with an ARNI rather than an ACE inhibitor or ARB.

The results from the PARADIGM-HF trial were so promising that the 2017 update recommends replacing ACE inhibitors and ARBs with the ARNI for patients with stage C heart failure with reduced ejection fraction in order to further reduce morbidity and mortality. To minimize the risk of angioedema caused by overlapping an ACE inhibitor and the ARNI during substitution, withhold the ACE inhibitor for at least 36 hours before starting the ARNI. ARNI therapy is contraindicated in patients with a history of severe angioedema, previous angioedema, and severe renal impairment.
of angioedema. Dual treatment with an ACE inhibitor (or ARB) and ARNI also is contraindicated. Patients already on an ACE inhibitor or ARB may be started on the ARNI at an oral dose of 49/51 mg twice daily; the dose should be doubled in 2 to 4 weeks to a target dose of 97/103 mg twice daily. BNP levels will increase in patients on an ARNI and decompensation should be measured with NT-proBNP.

Sinoatrial modulation Ivabradine is a new therapeutic agent that selectively inhibits the I, current in the sinoatrial node, reducing heart rate without lowering BP. The 2017 update supports using ivabradine to further reduce heart rates in patients with stage C heart failure with an LV ejection fraction of 35% or less. These patients should already be receiving optimal medical therapy, including a beta-blocker at the maximum tolerated dose and should be in normal sinus rhythm with a heart rate of 70 beats/minute or greater at rest. Ivabradine is available in three dosages (2.5, 5, and 7.5 mg), is given twice a day, and is titrated until the patient’s heart rate is between 50 and 60 beats/minute.

The Systolic Heart Failure Trial with the I Inhibitor Ivabradine Trial (SHIFT) investigated the effect of isolated heart rate reduction on outcomes in patients with heart failure. In SHIFT, the maximum studied dose of 7.5 mg of ivabradine twice daily significantly reduced hospitalizations for heart failure exacerbation by 18% when compared with placebo. Of the 6,558 patients involved in the study, only about 25% were receiving optimal doses of beta-blocker therapy. Given the mortality benefits of beta-blocker therapy, the 2017 update recommends maximizing beta-blockade, as tolerated, before assessing the patient’s resting heart rate and considering ivabradine therapy.

CONCLUSION
The 2017 ACC/AHA/HFSA guideline update recommends that to further reduce patient morbidity and mortality, clinicians replace an ACE inhibitor or ARB with the ARNI for patients with stage C heart failure with reduced ejection fraction who already are receiving adequate doses of an ACE inhibitor or ARB. Ivabradine can be effective as a supplemental medication for patients already maximized on beta-blockers who need additional heart rate reduction. Optimizing medical therapy, supporting behavior modification, treating comorbidities, and closely monitoring patients with heart failure will slow down disease progression and reduce the healthcare costs associated with this complex syndrome.

REFERENCES

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