NCPD 2.0 ANCC Contact Hours

Chronic Heart Failure

A Pharmacologic Review

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Chronic heart failure affects over 6 million Americans and is the main reason that people older than 65 years get admitted to the hospital (Centers for Disease Control and Prevention, 2020). Management of heart failure requires interdisciplinary efforts involving primary care physicians, cardiologists, nurses, and pharmacists among other providers. Nurses can play a key role in identifying patients at risk for heart failure exacerbation and are often at the front lines providing education regarding medication adherence. This article summarizes the medications used in chronic heart failure and describes common side effects, dosing considerations, and counseling points that are essential for appropriate management.

Introduction

According to the Centers for Disease Control and Prevention (CDC), approximately 6.2 million adults in the United States had heart failure between 2013 and 2016 (CDC, 2020). The average annual cost of cardiovascular disease reached over $300 billion in 2016–2017. In 2018, over 300,000 Americans died from heart failure (Virani et al., 2020). Of the total number of hospitalizations for heart failure, approximately half are characterized by heart failure with reduced ejection fraction (HFrEF) and the other half by heart failure with preserved ejection fraction (HFpEF) (Benjamin et al., 2019). Chronic heart failure has been defined as a global pandemic, affecting more than 26 million people worldwide. Given its significant effects on morbidity and mortality, it is necessary for healthcare providers to understand the various nonpharmacologic and pharmacologic options available to appropriately manage patients at home with chronic heart failure (Savarese & Lund, 2017).

Chronic heart failure (CHF) is characterized by a progressive inability of the heart to eject or receive blood resulting in characteristic signs and symptoms including shortness of breath, fatigue, dyspnea on exertion, peripheral edema, rales, and jugular venous distention. Chronic heart failure can occur on the right side, left side, or both sides of the heart. The type of heart failure will dictate which symptoms a patient may experience. Chronic heart failure is usually precipitated by a secondary cause such as a myocardial infarction or underlying chronic conditions such as long-standing hypertension, coronary artery disease, valvular deficiencies, or uncontrolled diabetes resulting in cardiac dysfunction. As cardiac output declines, multiple compensatory mechanisms are activated in attempts to improve cardiac output. Over time, these mechanisms can cause damage to myocytes, cardiac remodeling, and left ventricular hypertrophy (Francis, 2001).

The heart failure disease process includes neurohormonal changes, which lead to myocyte hypertrophy, activation of the renin–angiotensin–aldosterone system (RAAS), increase in salt and water retention, and an exaggerated response to natriuretic peptides. Initially, the levels of angiotensin II increase to promote vasoconstriction, increased aldosterone production from the adrenal glands, and sodium and fluid retention. These compensatory changes have a short-term beneficial effect in prompting an increase in cardiac output but have the detrimental effect of causing hypertension, peripheral edema, and pulmonary edema. This cascade of events causes significant adverse effects on the cardiac system including left ventricular hypertrophy and cardiac fibrosis. The cycle continues and what began as a compensatory mechanism eventually results in major myocardial damage (Francis, 2001).

The left ventricular ejection fraction is a measure of the amount of blood pumped out of the left ventricle with each contraction and is used to categorize patients with heart failure into one of three major categories as denoted in Table 1. The patient's heart failure classification will ultimately determine the approach for pharmacologic management (Groenewegen et al., 2020).

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Table 1. Heart Failure Classification

Ejection Fraction (EF)	Heart Failure Classification
≥50%	Heart failure with preserved EF
41%–49%	Heart failure with mid-range EF
≤40%	Heart failure with reduced EF

Note. Data from Yancy et al. (2013).

Table 2 has a list of common risk factors for the development of CHF. Hypertension, however, may be the single most important contributor to the development of heart failure, as higher levels of systolic and diastolic blood pressures have been associated with development and progression of heart failure and worsened outcomes. Long-term treatment of hypertension can reduce the risk of CHF by approximately 50% according to some studies (Shah et al., 2017). American College of Cardiology/American Heart Association (ACC/AHA) guidelines for hypertension advise the use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), dihydropyridine (DHP) calcium channel blockers, and thiazide diuretics as first-line agents in the treatment of hypertension (Yancy et al., 2013). Among African American patients, the preferred first-line therapies are limited to DHP calcium channel blockers and thiazide diuretics. Nonpharmacologic and pharmacologic therapies should be used to target a blood pressure goal of less than 130/80 mmHg according to the ACC/AHA. Table 3 includes a list of nonpharmacologic strategies that can be utilized. Nurses can play a crucial role in preventing the development of heart failure by counseling patients on medication adherence and assisting them with managing their chronic conditions. Nurses also play a key role in educating patients on signs and symptoms of heart failure and are often the first source of patient education (Yancy et al., 2013).

Pharmacologic Therapy

Patients with CHF are typically treated with multiple agents to optimize outcomes and manage their symptoms. Table 4 summarizes these medications. Multiple drug classes have been proven to reduce mortality in patients with HFrEF including ACE inhibitors, ARBs, aldosterone antagonists, beta blockers, and angiotensin receptor–neprilysin inhibitor (ARNi) and most recently, sodium–glucose cotransport 2 (SGLT2) inhibitors (Shah et al., 2017; Yancy et al., 2017). No drug therapies to date have consistently demonstrated a mortality benefit in patients with HFpEF.

Table 2. Risk Factors for Heart Failure

Modifiable	Nonmodifiable
Hypertension	Older than 65 years
Diabetes mellitus	African American race
Metabolic syndrome	Male sex
Atherosclerotic disease	
Obesity	
Medications (thiazolidinediones, nondihydropyridine calcium channel blockers, TNF-α inhibitors, among many other medications)	

Note. TNF-α = tumor necrosis factor-α. Data from Yancy et al. (2013).

Table 3. Nonpharmacologic Therapy

Physical activity	Minimum of 150 minutes per week of moderate-intensity exercise (biking, walking quickly, swimming, etc.) in patients who are able
Weight reduction	Goal to reduce BMI to less than 30 kg/m^2
Sodium restriction	Goal to reduce sodium intake to less than 2,000 mg/day
Management of sleep disorders	Consider the use of continuous positive airway pressure devices, if applicable

Note. BMI = body mass index. Data from Yancy et al. (2013).

ACE Inhibitors and ARBs

Angiotensin II is a potent vasoconstrictor within the body that causes elevated blood pressure, hypertrophy of vascular tissues, and aldosterone secretion. The ACE inhibitors work by inhibiting the formation of angiotensin II, which ultimately allows for increased vasodilation, decrease in aldosterone, and reduction in fluid retention, and decreases the workload of the heart. Contraindications to ACE inhibitor therapy include a history of angioedema, hyperkalemia, acute kidney injury, and pregnancy. It is important to note that when patients begin therapy with an ACE inhibitor, the serum creatinine can increase up to 30% as a result of the hemodynamic effects of this class. Unless serum creatinine increases beyond 30%, this does not warrant discontinuation of the medication, rather should be monitored closely for resolution. Angiotensin receptor blockers also work by blocking the activity of angiotensin II at the angiotensin receptor and have a similar effect on vasodilation, fluid retention, and mortality benefit. Although ACE inhibitors are known to cause nonproductive cough in many patients through an inhibition of kininase, ARBs do not affect this enzyme, so cough is not considered an adverse effect of ARBs. Aside from this distinction, ARBs have a similar side effect profile in comparison to ACE inhibitors. Blood pressure, renal function, and serum potassium should be monitored closely 1–2 weeks after initiating therapy or increasing the dose for either class (Shah et al., 2017).

Angiotensin Receptor–Neprilysin Inhibitors

ARNis are a combination of an ARB (valsartan) plus a neprilysin inhibitor (sacubitril). Entresto (sacubitril/valsartan) is currently the only ARNi on the market at this time and is approved only for HFrEF. Sacubitril inhibits the effects of neprilysin, an enzyme responsible for degrading peptides in the body that have beneficial effects including vasodilation, diuresis, and prevention of cardiac remodeling. Importantly, the effects of sacubitril on neprilysin can lead to increases in angiotensin II, which is why the addition of an ARB is needed to suppress the RAAS. If switching a patient from an ACE

Table 4. Pharmacologic Therapy for Heart Failure With Reduced Ejection Fraction

Category	Most Commonly Utilized Drugs	Mortality Benefit	Adverse Effects	Monitoring
ACE inhibitors	Lisinopril Enalapril	Yes	Dry cough Angioedema Hyperkalemia Acute kidney injury	Blood pressure Serum creatinine Potassium
ARBs	Losartan Valsartan	Yes	Angioedema Hyperkalemia Acute kidney injury	Blood pressure Serum creatinine Potassium
ARNi	Sacubitril/valsartan	Yes	Angioedema Hyperkalemia Acute kidney injury	Blood pressure Serum creatinine Potassium
Aldosterone antagonists	Spironolactone Eplerenone	Yes	Gynecomastia Hyperkalemia Acute kidney injury	Blood pressure Serum creatinine Potassium
Beta blockers	Carvedilol Metoprolol succinate Bisoprolol	Yes	Bradyarrhythmia Bronchospasm Fatigue Masking of hypoglycemia in diabetic patients	Heart rate Blood pressure
SGLT2 inhibitors	Empagliflozin Dapagliflozin	Yes	Hypotension Electrolyte abnormalities Urinary tract infections	Serum creatinine Serum electrolytes Blood pressure
Loop diuretics	Bumetanide Furosemide Torsemide	No	Sun sensitivity Dehydration Electrolyte abnormalities Acute kidney injury	Serum creatinine Serum electrolytes Volume status Blood pressure

Note. ACE = angiotensin-converting enzyme; ARBs = angiotensin receptor blockers; ARNi = angiotensin receptor–neprilysin inhibitor; SGLT2 = sodium–glucose cotransport 2. Data from Yancy et al. (2017) and Shah et al. (2017).

inhibitor to an ARNi, a 36-hour washout period is required to reduce the risk of angioedema (Shah et al., 2017). Like ACE inhibitors and ARBs, monitoring of blood pressure, renal function, and serum potassium is important in patients receiving ARNis. In clinical practice, patients are often initiated on an ACE inhibitor or ARB first, and then converted to an ARNi as was done in clinical trials. Importantly, patients should never utilize an ACE, ARB, and ARNi, in combination and should only be prescribed one of these three agents at a time.

Beta Blockers

Beta blockers work by blocking the beta-1 adrenergic receptors located on the heart. This effect helps to prevent cardiac remodeling that is caused by the RAAS and sympathetic nervous system. Only three beta blockers have been shown to have a mortality benefit in patients with HFrEF: carvedilol, metoprolol succinate, and bisoprolol. Beta blockers should be initiated at low doses and titrated slowly to target doses if tolerable. Similarly, if beta blockers need to be discontinued, the dose should be tapered off slowly over an extended period to reduce risk of withdrawal syndrome (Shah et al., 2017). Patients should be counseled that fatigue is common when initiating therapy but should improve within 1–2 weeks. Precaution should be used in patients with asthma or chronic obstructive pulmonary disease who need beta blockade, as beta blockers (especially at higher doses) can potentially block beta-2 receptors on the lung causing bronchoconstriction or bronchospasm. Carvedilol, a nonselective beta blocker, is often avoided in patients with these lung conditions in favor of beta-1 selective beta blockers such as metoprolol succinate or bisoprolol. Heart rate and blood pressure should be monitored 1–2 weeks after initiating therapy or increasing the dose.

Aldosterone Antagonists

Aldosterone antagonists, also known as mineralocorticoid receptor antagonists (MRAs), work by inhibiting the effects of aldosterone, which include myocardial fibrosis, vascular injury, and cardiac remodeling (Li et al., 2018). The use of MRAs may potentially slow the progression of disease and prevent or reverse cardiac remodeling. Spironolactone is one of the most commonly used MRAs. It is structurally very similar to progesterone, which contributes to the adverse effects including gynecomastia and amenorrhea due to concurrent blockade of the androgen receptor. These effects are not seen with the other MRA, eplerenone, as eplerenone is more selective to the aldosterone receptor. Both agents are potassium sparing and can induce acute kidney injury; careful monitoring of renal function and potassium levels is warranted (Shah et al., 2017).

Sodium–Glucose Cotransport 2 Inhibitors

Sodium–glucose cotransporter 2 (SGLT2) inhibitors are a class of medications commonly used to treat type 2 diabetes mellitus. Examples of SGLT2 inhibitors include dapagliflozin, empagliflozin, and canagliflozin.

Recently, evidence has been increasing to support the use of this drug class in HFrEF. In May 2020, the Food and Drug Administration approved the SGLT2 inhibitor, dapagliflozin, for the treatment of HFrEF based on the results of Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction (DAPA-HF) trial (Zannad et al., 2020). This study found that dapagliflozin had a favorable effect in reducing both cardiovascular death and worsening heart failure in patients with and without diabetes. Similar outcomes have been seen with empagliflozin. Adverse reactions of this class include an increased risk of urinary tract infections, hypotension, and electrolyte imbalances. According to the most recent revision of the ACC/AHA guidelines in 2022, SGLT2 inhibitors are to be included as a part of guideline-directed medical therapy for patients with HFrEF (Heidenreich et al., 2022; Rosano et al., 2020).

The agents discussed thus far have all demonstrated an effect on mortality in HFrEF, and although this effect is not seen with loop diuretics (reviewed next), they continue to be a mainstay of treatment in these patients.

Loop Diuretics

Loop diuretics are a mainstay of treatment in the management of heart failure to reduce peripheral and pulmonary edema. It is important to note, however, that diuretics have not been shown to exhibit a mortality benefit; instead, diuretics are initiated and titrated to control symptoms of congestion. Loop diuretics are preferred in the setting of HFrEF given their potent diuretic effect. Thiazide diuretics, while less potent than loop diuretics, can be used in combination with loop diuretics to stimulate further diuresis in patients on maximum doses of loop diuretics (Shah et al., 2017). Blood pressure, renal function, and serum electrolytes should be monitored closely for patients treated with diuretics. Patients taking loop diuretics should monitor their body weight daily as a marker for fluid retention or loss. Additionally, patients taking loop diuretics should be counseled to take diuretics in the morning (to avoid the need to wake up and urinate at night). Loop diuretics also carry the potential to cause dehydration, increased sun sensitivity, and muscle cramps especially when electrolyte abnormalities are not addressed.

In summary, ACE inhibitors, ARBs, ARNis, beta blockers, and MRAs and now SGLT2 inhibitors form the backbone of therapy in patients with HFrEF due to their favorable effects on morbidity and mortality.

Special Populations

Additional medications may be utilized in CHF in specific patient populations Table 5 summarizes these medications. For example, vasodilators such as hydralazine and isosorbide dinitrate have been shown to reduce mortality in HFrEF and especially among African American patients. The pill burden (two tablets three or four times per day) and adverse effect profile limit the utility of this regimen. These agents work by promoting vasodilation and relaxing vascular smooth muscle. Importantly, phosphodiesterase-5 inhibitors primarily used for treatment of erectile dysfunction (sildenafil, tadalafil, and vardenafil) are contraindicated with the use of isosorbide dinitrate and other nitrates due to the risk of symptomatic hypotension. Digoxin has been shown to reduce the rate of hospitalizations in patients with HFrEF. It may be favorable in patients with HFrEF and concomitant atrial fibrillation due to its effects on lowering heart rate. Ivabradine can be used to reduce heart rate in patients who have not met their heart rate goal despite using maximum doses of beta blockers or who are unable to tolerate beta blockers (Shah et al., 2017).

Emerging Therapies

Vericiguat is a soluble guanylate cyclase activator that works to sensitize guanylate cyclase to endogenous nitric oxide ultimately increasing smooth muscle relaxation and vasodilation. The Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction (VICTORIA) study found that vericiguat reduced the incidence of death from cardiovascular causes or hospitalizations for heart failure as compared with placebo. Although this trial showed promising results, more data

Table 5. Medications Used in Special Populations

Category	Drug Name	Mortality	Adverse Effects	Monitoring
Vasodilators	Hydralazine + Isosorbide dinitrate	Yes	Headache Dizziness Nausea Chest pain Drug-induced lupus-like syndrome	Blood pressure Heart rate
Cardiac glycoside	Digoxin	No	Bradycardia Digoxin toxicity (nausea, vomiting, visual disturbances, yellow or blurred vision, and arrhythmias)	Heart rate Cardiac rhythm Serum creatinine Serum electrolytes (K, Mg) Serum digoxin levels
I(f) inhibitor	Ivabradine	No	Bradycardia Hypertension Atrial fibrillation	Heart rate Blood pressure Cardiac rhythm

Note. Data from Shah et al. (2017).

Table 6. Guideline-Directed Medical Therapy: Target Doses

Category	Drug Name	Starting Dose	Target Dose
ACE inhibitors	Lisinopril	2.5–5 mg daily	40 mg daily
	Enalapril	2.5 mg twice a day	20 mg twice a day
ARBs	Losartan	25–50 mg daily	150 mg daily
	Valsartan	20–40 mg twice a day	160 mg twice a day
ARNi	Sacubitril/valsartan	49/51 mg twice a day	97/103 mg twice a day
Beta blockers	Bisoprolol	1.25 mg daily	10 mg daily
	Metoprolol succinate	12.5–25 mg daily	200 mg daily
	Carvedilol	3.125 mg twice a day	50 mg twice a day
Aldosterone antagonists	Spironolactone	12.5–25 mg daily	25 mg daily or twice a day
SGLT2 inhibitors	Empagliflozin	10 mg once daily	10 mg once daily
	Dapagliflozin		

Note. ACE = angiotensin-converting enzyme; ARBs = angiotensin receptor blockers; ARNi = angiotensin receptor–neprilysin inhibitor; SGLT2 = sodium–glucose cotransport 2. Data from Yancy et al. (2017) and Shah et al. (2017).

are needed to determine the place on therapy of vericiguat in CHF (Armstrong et al., 2020).

Table 6 depicts common medications of each drug class and the target doses as defined in the ACC/AHA guidelines for HFrEF. This list is not all inclusive as there are additional agents available within each drug class. The mortality benefit seen with these drug classes was seen at particular doses achieved in clinical trials. For this reason, these medications are usually titrated to target doses as opposed to titrated to a goal blood pressure or heart rate. Nurses are often assisting patients with filling up pillboxes and providing education. A knowledge of these target doses can help nurses to identify patients who may benefit from medication titration.

Conclusions

Although the management of HFrEF is centered around pharmacologic therapies that have been proven to reduce morbidity and mortality, the management of HFpEF lacks similar data. To date, there have been no pharmacologic therapies with proven effects on morbidity and mortality in HFpEF patients. For this reason, HFpEF is currently managed primarily by treating comorbid conditions such as hypertension, diabetes, and hyperlipidemia. Currently, there are some data to suggest that spironolactone and SGLT2 inhibitors may reduce the risk of heart failure hospitalization in patients with HFpEF (Pitt et al., 2014; Anker et al., 2021). The ACC/AHA guidelines support the use of spironolactone in patients with HFpEF to reduce hospitalizations based on the results of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) study. However, there has been much debate regarding the methods of this study, specifically the varying criteria used to identify patients with HFpEF as well as varying medication adherence rates across the included cohorts (Pitt et al., 2014). Although the therapy options in the setting of HFrEF have been thoroughly developed, therapy options for HFpEF remain under evaluation.

All in all, CHF greatly affects morbidity and mortality in patients and burdens the healthcare system. To prevent the development of heart failure, emphasis should be placed on managing risk factors for development of disease. For patients with confirmed diagnosis of HFrEF, guideline-directed medical therapy should be utilized to reduce morbidity and mortality. More information regarding targeted management of HFpEF is anticipated in the coming years. Nursing staff can play a key role in providing patient education regarding signs and symptoms of heart failure and medication adherence and can work with the healthcare team to identify patients who may benefit from medication adjustment or who are at risk for hospitalization.

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