

# Heart Failure: A Class Review of Pharmacotherapy

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## INTRODUCTION

Heart failure (HF) affects more than 6.5 million people in the United States and has a 50% mortality rate within five years of diagnosis.<sup>1</sup> The lifetime risk of HF at 45 years of age is 30% for white men and 32% for white women.<sup>2</sup> HF is a progressive disease that can result from any structural or functional changes of the heart, leading to the impairment of ventricular filling or ejection of blood. As a consequence, the heart cannot pump blood fast enough to meet the demands of the body.<sup>3</sup> Typical symptoms of HF include dyspnea and fatigue. The symptoms that present are usually nonspecific to HF but can lead to the review of more specific signs, such as elevated jugular venous pressure or displacement of the apical impulse, and can guide a practitioner to review radiological data consistent with HF.

Imaging plays an important role in the diagnosis of HF, with echocardiography being the gold standard. Transthoracic echocardiography is the method of choice for assessment of myocardial systolic and diastolic function of both the left and right ventricles.<sup>4</sup> Once the diagnosis is confirmed, the goals of treatment are to improve clinical status, functional capacity, and quality of life; to prevent hospital admission; and to reduce mortality.

The 2013 guidelines of the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) defined two types of HF: preserved ejection fraction (HFpEF) and reduced ejection fraction (HFrEF). A preserved ejection fraction (EF) is 50% or greater, while reduced EF was defined as 40% or less. Patients with an EF of more than 40% but less than 50% represent an intermediate group whose treatment is similar to HFpEF.<sup>3</sup>

In addition to HF type, patients can be assigned a class and/or stage of HF. The New York Heart Association (NYHA) defines four classes of HF:<sup>3</sup>

- Class I: No physical limitation; ordinary physical activity does not cause HF symptoms
- Class II: No symptoms at rest, but ordinary physical activities cause HF symptoms

- Class III: No symptoms at rest, but less-than-ordinary physical activities cause HF symptoms
- Class IV: Symptoms of HF at rest

The ACCF/AHA also defines four stages of HF:<sup>3</sup>

- Stage A: At high risk for HF but without structural heart disease or symptoms of HF
- Stage B: Structural heart disease but without signs or symptoms of HF
- Stage C: Structural heart disease with prior or current symptoms of HF
- Stage D: Refractory HF requiring specialized interventions

The NYHA classes focus on exercise capacity and the symptomatic status of the disease, whereas the ACCF/AHA stages evaluate the development and progression of the disease.

After a patient has been diagnosed with a type, stage, and class, treatment can be determined. First-line drug therapy for all patients with HFrEF should include an angiotensin-converting enzyme (ACE) inhibitor and beta blocker.<sup>5</sup> These medications have been shown to decrease morbidity and mortality.<sup>5</sup>

However, the 2016 “Focused Update on New Pharmacological Therapy for Heart Failure” from the ACCF, AHA, and Heart Failure Society of America (HFSA) changed how patients are managed in stage C with HFrEF. The new guidelines focused on two new classes of medications: an angiotensin receptor-neprilysin inhibitor (ARNI) (valsartan/sacubitril [Entresto, Novartis]) and a sinoatrial node modulator (ivabradine [Corlanor, Amgen]). A recent study found valsartan/sacubitril to be superior to the ACE inhibitor enalapril when added to standard therapy, including a beta blocker and diuretics, in reducing the risk of death and hospitalization.<sup>6</sup> Ivabradine also reduced the risk of hospitalization for worsening heart failure and the risk of cardiovascular death.<sup>5</sup>

With the release of the 2016 ACCF/AHA/HFSA update, a new look at all of the medication classes and trials is pertinent. This article will focus on pharmacological options available for the treatment of HF.<sup>6</sup>

## ACE INHIBITORS

The ability of ACE inhibitors, such as enalapril and lisinopril, to reduce mortality when taken concurrently with other HFrEF medications has made this class of medications the mainstay for treatment of HFrEF in patients free from any contraindications to their use.<sup>3,6</sup>

ACE inhibitors decrease peripheral resistance and reduce the load on the failing myocardium by inhibiting the conversion of angiotensin I to angiotensin II, thus preventing vasoconstriction.

**Disclosures:** Dr. Srivastava has been a speaker for Novartis-funded conferences. The other authors report no commercial or financial interests in regard to this article.

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tion and causing relaxation of the vasculature. The efficacy of ACE inhibitors has been proven over several decades. Major trials analyzing ACE inhibitors in HF $\nabla$ EF have utilized them in addition to standards of care such as digoxin, vasodilators, loop diuretics, potassium-sparing diuretics, and beta blockers.<sup>7–10</sup> The CONSENSUS trial, which compared enalapril with placebo in addition to standard of care, showed that enalapril reduced overall mortality risk by 27% and significantly decreased the number of patients with HF $\nabla$ EF progression.<sup>7</sup> The SOLVD trial demonstrated that, compared with placebo, treatment with enalapril over the course of three years prevented 50 premature deaths and 350 hospitalizations per 1,000 patients.<sup>8</sup> Collectively, these trials suggest that ACE inhibitors, when taken concurrently with other HF $\nabla$ EF medications, provide significant reductions in morbidity and mortality. These benefits have been shown to remain clinically significant throughout long courses of therapy.<sup>10</sup>

Contraindications to ACE inhibitor therapy include hypersensitivity, previous angioedema from ACE inhibitor use, or concomitant use with aliskiren. Adverse effects to monitor for in patients using ACE inhibitors include headache, cough, diarrhea, dizziness, and fatigue; most of these effects are transient and mild. More serious events include reversible increases in serum creatinine (SCr) and symptomatic hypotension, both related to the hemodynamic effects of ACE inhibitors.<sup>9</sup> While the exact number is not agreed upon, an SCr increase of up to 30% is regarded as acceptable and does not warrant stopping ACE inhibitor therapy. In trials, small but significant increases in serum potassium were observed.<sup>7</sup> Caution should be exercised in patients with pre-existing hypotension, those with baseline hyperkalemia (potassium greater than 5 mEq/L), and those receiving concomitant potassium supplements or potassium-sparing diuretics.<sup>7</sup>

The usual dosing strategy for ACE inhibitors is to initiate at a low dose and double the dose every one to two weeks, if tolerated, up to the prespecified target dose (Table 1). Monitor patients for hypotension, potassium levels, and decreased renal function during the titration period to assess tolerability. Patients with pre-existing conditions that put them at a higher risk for side effects (sodium levels less than 130 mEq/L, creatinine clearance [CrCl] less than 30 mL/min, an increase in diuretic dose in the past week, or treatment with a potassium-sparing diuretic) may be initiated at a lower dose.<sup>11–18</sup>

### ANGIOTENSIN RECEPTOR BLOCKERS

Angiotensin receptor blockers (ARBs) inhibit the renin-angiotensin-aldosterone system (RAAS) by blocking the binding of angiotensin II to its receptor, which in turn leads to vasoconstriction and prevents the release of aldosterone. Although their mechanism of action is similar to that of ACE inhibitors, ARBs do not cause an inhibition of kininase, which reduces the incidence of cough in comparison with ACE inhibitors. The 2016 ACCF/AHA/HFSA guidelines recommend that ARBs be used to reduce morbidity and mortality in patients who are intolerant of ACE inhibitors because of cough or angioedema or in patients who are tolerating ARBs for another indication. In addition, the 2016 guidelines recommend that ARBs be used with caution in patients with a history of angioedema with ACE inhibitors because of the risk of cross-reaction.

For patients with HF $\nabla$ EF NYHA class II or III, the guidelines recommend replacing ARB therapy with an ARNI, which will be discussed later in this article.<sup>6</sup>

Placebo-controlled trials have shown that the use of ARBs reduces hospitalization and mortality. The 2003 Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM Alternative) study evaluated whether candesartan could improve cardiovascular outcomes compared with placebo, including the composite endpoint of cardiovascular death or hospital admission in patients with symptomatic HF with an EF of 40% or less who were intolerant of ACE inhibitors. The primary outcome of cardiovascular death or hospitalization for HF occurred in 33% of candesartan patients versus 40% of placebo patients (covariate adjusted hazard ratio [HR], 0.70; 95% confidence interval [CI], 0.60–0.81;  $P < 0.001$ ).<sup>19</sup>

It is important to monitor patients on ARB therapy closely and titrate the dose as tolerated. The Heart Failure End Point Evaluation of Angiotensin II Antagonist Losartan (HEAAL) study evaluated more than 3,800 patients with HF $\nabla$ EF NYHA class II–IV who were intolerant of ACE inhibitors; participants were randomly assigned to losartan 150 mg daily or 50 mg daily. The primary endpoint, death or admission for HF, occurred in 43% of patients in the 150-mg group versus 46% of patients in the 50-mg group (HR, 0.90; 95% CI, 0.82–0.99;  $P = 0.027$ ).<sup>20</sup> This study, although specific to losartan dosing, shows the value of uptitrating ARB dosing for maximal benefit. When initiating ARB therapy, start with a low dose and titrate up as tolerated by doubling the dose to the target.

Baseline renal function and serum potassium should be established prior to initiating ARB therapy. ARBs can cause hyperkalemia due to the inhibition of aldosterone, often in combination with other predisposing factors such as combination medications or physiological conditions that have reduced serum aldosterone concentrations. It is important to monitor these assays regularly to identify abnormalities because modifications of the patient's drug therapy or dietary intake of potassium may be required.<sup>21</sup>

### BETA BLOCKERS

The beneficial effect of beta blockade in HF $\nabla$ EF has been documented for more than 40 years.<sup>22</sup> Since 1975, data have shown that the use of bisoprolol, carvedilol, or sustained-release metoprolol succinate reduces morbidity and mortality in patients with HF $\nabla$ EF. These are the only beta blockers tested in large clinical trials to show a mortality benefit, which led to their inclusion in the HF guidelines as first-line agents in all patients with HF $\nabla$ EF to reduce morbidity and mortality unless contraindicated.<sup>3,23–25</sup> These three agents share a common pathway: They all block the  $\beta_1$ -adrenergic receptor located on the heart. HF $\nabla$ EF stimulates the RAAS and sympathetic system in order to compensate for the reduced EF. However, this activation may accelerate ventricular remodeling. By blocking  $\beta_1$  receptors, these beta blockers prevent ventricular remodeling promoted by the stimulated RAAS and sympathetic system. While metoprolol and bisoprolol are selective for the  $\beta_1$  receptor, carvedilol also blocks the  $\beta_2$  and  $\alpha_1$  receptors, leading to vasodilation.<sup>24,26</sup> The COPERNICUS study had patients double their dose of carvedilol until a mean dose of 37 mg per day was achieved, showing an all-cause mortality of 11.4% versus

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**Table 1 Oral Therapies for the Treatment of Heart Failure**

Medication	Initial Dose	Target Dose*	Adverse Effects	Contraindications		
<b>Angiotensin-Converting Enzyme Inhibitors<sup>3,11–18</sup></b>						
Captopril	6.25–25 mg TID	50 mg TID	<ul style="list-style-type: none"> <li>• Hypotension</li> <li>• SCr/BUN increase</li> <li>• Hyperkalemia</li> <li>• Cough</li> </ul>	<ul style="list-style-type: none"> <li>• Hypersensitivity</li> <li>• Previous angioedema due to any ACE inhibitor</li> </ul>		
Enalapril	2.5 mg BID	20 mg BID				
Fosinopril	5–10 mg daily	40 mg daily				
Lisinopril	2.5–5 mg daily	40 mg daily				
Perindopril	2 mg daily	16 mg daily				
Quinapril	5 mg BID	20 mg BID				
Ramipril	1.25–2.5 mg daily	10 mg daily				
Trandolapril	1 mg daily	4 mg daily				
<b>Angiotensin Receptor Blockers<sup>59–61</sup></b>						
Candesartan	4–8 mg daily	32 mg daily	<ul style="list-style-type: none"> <li>• Hypotension</li> <li>• SCr/BUN increase</li> <li>• Hyperkalemia</li> </ul>	<ul style="list-style-type: none"> <li>• Hypersensitivity</li> <li>• Concomitant use with aliskiren in patients with diabetes</li> </ul>		
Losartan	25–50 mg daily	150 mg daily				
Valsartan	20–40 mg BID	160 mg BID				
<b>Beta Blockers<sup>62–65</sup></b>						
Bisoprolol	1.25 mg daily	10 mg daily	<ul style="list-style-type: none"> <li>• Hypotension</li> <li>• First-degree heart block</li> <li>• Edema</li> <li>• Dizziness</li> <li>• Abdominal pain/diarrhea</li> </ul>	<ul style="list-style-type: none"> <li>• Severe bradycardia</li> <li>• Second- or third-degree heart block in the absence of a pacemaker</li> <li>• Cardiogenic shock</li> <li>• Decompensated HFrEF</li> <li>• Sick sinus syndrome</li> </ul>		
Carvedilol	3.125 mg BID	50 mg BID				
Carvedilol CR	10 mg daily	80 mg daily				
Metoprolol succinate	12.5–25 mg daily	200 mg daily				
<b>Loop Diuretics<sup>43,66–68</sup></b>						
Bumetanide	0.5–1.0 mg daily or BID	10 mg daily	<ul style="list-style-type: none"> <li>• Hypotension/dizziness</li> <li>• Fluid loss</li> <li>• Hypokalemia, hypocalcemia, hypomagnesemia, hyponatremia, hypochloremia</li> <li>• Hyperuricemia</li> <li>• Cramping/diarrhea</li> <li>• Nephrotoxicity/ototoxicity</li> </ul>	<ul style="list-style-type: none"> <li>• Hypersensitivity</li> <li>• Anuria</li> </ul>		
Furosemide	20–40 mg daily or BID	600 mg daily				
Torsemide	10–20 mg daily	200 mg daily				
Ethacrynic acid	25–50 mg daily	100 mg BID				
<b>Thiazide Diuretics Used in Combination With Loop Diuretics<sup>69,70</sup></b>						
Metolazone	2.5–10 mg daily + loop diuretic	NA	<ul style="list-style-type: none"> <li>• Hypotension</li> <li>• Dizziness</li> <li>• Gout attacks</li> <li>• Hypercalcemia</li> <li>• BUN increase</li> </ul>	<ul style="list-style-type: none"> <li>• Hypersensitivity</li> <li>• Anuria</li> <li>• Hydrochlorothiazide: CrCl ≤ 10 mL/min</li> </ul>		
Hydrochlorothiazide	25–100 mg daily or BID + loop diuretic	NA				
<b>Aldosterone Antagonists<sup>30,31</sup></b>						
	CrCl < 50	CrCl > 50	CrCl < 50	CrCl > 50	<ul style="list-style-type: none"> <li>• Hyperkalemia</li> <li>• Diarrhea</li> <li>• Impaired renal function</li> <li>• Dizziness</li> <li>• Fatigue</li> <li>• Spironolactone: gynecomastia</li> </ul>	<ul style="list-style-type: none"> <li>• Spironolactone: acute renal insufficiency, anuria, or significant renal dysfunction</li> <li>• Eplerenone: serum potassium &gt; 5.5 mEq/L at initiation, CrCl &lt; 30 ml/min, concomitant use of strong CYP3A4 inhibitors</li> </ul>
Spironolactone	12.5 mg daily or every other day	12.5–25 mg daily	12–25 mg daily	25 mg daily or BID		
Eplerenone	25 mg every other day	25 mg daily	25 mg daily or BID	50 mg daily		

*table continues*

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**Table 1 Oral Therapies for the Treatment of Heart Failure (continued)**

Medication	Initial Dose	Target Dose*	Adverse Effects	Contraindications
<b>Vasodilators<sup>3,44</sup></b>				
Hydralazine	25–50 mg TID–QID	300 mg daily in divided doses	<ul style="list-style-type: none"> <li>• Hypotension</li> <li>• Headache</li> <li>• Dizziness</li> <li>• Asthenia</li> <li>• Nausea</li> </ul>	<ul style="list-style-type: none"> <li>• Allergy to nitrates</li> <li>• PDE5 inhibitors (avanafil, sildenafil, tadalafil, vardenafil)</li> <li>• Riociguat</li> </ul>
Isosorbide dinitrate	20–30 mg TID–QID	120 mg daily in divided doses		
Fixed-dose combination	37.5 mg hydralazine/20 mg isosorbide dinitrate TID	75 mg hydralazine/40 mg isosorbide dinitrate TID		
<b>Digoxin<sup>48</sup></b>				
Digoxin	0.125–0.25 mg daily	0.25 mg daily (may be lower in patients older than 70 years of age or patients with renal dysfunction to maintain serum concentration between 0.5–0.9 ng/mL)	<ul style="list-style-type: none"> <li>• Arrhythmias</li> <li>• Heart block</li> <li>• Nausea/vomiting</li> <li>• Diarrhea</li> <li>• Anorexia</li> <li>• Visual changes</li> <li>• Headache</li> <li>• Gynecomastia (long-term use)</li> <li>• Confusion</li> </ul>	<ul style="list-style-type: none"> <li>• Hypersensitivity</li> <li>• Ventricular fibrillation</li> </ul>
<b>I(f) Inhibitor<sup>53</sup></b>				
Ivabradine	5 mg BID	7.5 mg BID	<ul style="list-style-type: none"> <li>• Bradycardia</li> <li>• Atrial fibrillation</li> <li>• Phosphenes (transient enhanced brightness in restricted area of visual field)</li> <li>• Blurred vision</li> </ul>	<ul style="list-style-type: none"> <li>• Acute decompensated HF/EF</li> <li>• BP &lt; 90/50 mm Hg</li> <li>• Sick sinus syndrome, sinoatrial block, or third-degree AV block without functioning demand pacemaker</li> <li>• Resting HR &lt; 60 bpm prior to treatment</li> <li>• Severe hepatic impairment</li> <li>• Pacemaker dependence</li> <li>• Concomitant use with strong CYP3A4 inhibitors</li> </ul>
<b>Angiotensin Receptor-Neprilysin Inhibitor<sup>58</sup></b>				
Sacubitril/valsartan	49 mg/51 mg BID	97 mg/103 mg BID	<ul style="list-style-type: none"> <li>• Hypotension</li> <li>• Hyperkalemia</li> <li>• SCr increase</li> <li>• Dizziness</li> <li>• Cough</li> </ul>	<ul style="list-style-type: none"> <li>• Previous angioedema due to any ACE inhibitor or ARB</li> <li>• Concomitant use of ACE inhibitors or use within the previous 36 hours</li> <li>• Concomitant use of aliskiren in diabetic patients</li> </ul>
<p>ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; AV = atrioventricular; BID = two times daily; BP = blood pressure; bpm = beats per minute; BUN = blood urea nitrogen; CrCl = creatinine clearance; CYP3A4 = cytochrome P450 3A4; HF/EF = heart failure with reduced ejection fraction; HR = heart rate; I(f) = channel through which “funny” or pacemaker current flows in the heart; NA = not applicable; PDE5 = phosphodiesterase type 5; QID = four times daily; SCr = serum creatinine; TID = three times daily.</p> <p>* Dose recommended for heart failure patients; this dose may be higher for other indications.</p>				

18.5% in the placebo group ( $P = 0.00013$ ). Bisoprolol was evaluated in the CIBIS-II trial, leading to all-cause mortality of 8.8% versus 13.2% in the placebo group ( $P < 0.0001$ ). Finally, the MERIT-HF trial compared metoprolol succinate with placebo in patients on baseline ACE-inhibitor and diuretic therapy to evaluate all-cause mortality (7.2% versus 11%;  $P = 0.00009$ ) and all-cause mortality plus all-cause hospitalization (32% versus 38%;  $P < 0.001$ ).<sup>4,25</sup>

Beta blockers should be initiated at low doses and titrated slowly to target doses if tolerable (Table 1). Adverse events include fluid retention and worsening HF/EF, fatigue, bradycardia or heart block, and hypotension. The fluid retention or worsening HF/EF associated with beta blockers do not generally warrant the permanent withdrawal of treatment. Beta-blocker-induced bradycardia is generally asymptomatic and thus requires no treatment; however, if the bradycardia

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is accompanied by dizziness, lightheadedness, or second- or third-degree heart block, the dose of the beta blocker should be decreased. Patients should be monitored closely for changes in vital signs and symptoms during this titration period. If the target doses are not tolerated, the highest tolerated dose should be continued.<sup>3</sup>

### ALDOSTERONE ANTAGONISTS

Aldosterone receptor antagonists (also called mineralocorticoid receptor antagonists [MRAs]) are recommended for NYHA class II–IV HF patients with an EF of 35% or less, glomerular filtration rate of at least 30 mL/min/1.73 m<sup>2</sup>, and a potassium level of 5.0 mEq/dL or lower.<sup>3</sup> Studies have demonstrated that aldosterone receptor antagonists (when given in conjunction with ACE inhibitors and beta blockers) reduce the risk of morbidity and mortality in patients with NYHA class III–IV HF with an EF of 35% or less.<sup>27,28</sup> Further studies found similar benefits in NYHA class II HF patients with an EF of 35% or less.<sup>29</sup>

Two aldosterone receptor antagonists are available in the United States—spironolactone and eplerenone. Spironolactone is a nonselective aldosterone antagonist, while eplerenone is selective to the aldosterone receptor.<sup>30,31</sup> Aldosterone is an endogenous steroid hormone that increases sodium retention and facilitates magnesium/potassium loss. Aldosterone may ultimately cause myocardial fibrosis, vascular injury, direct vascular damage, and baroreceptor dysfunction leading to the development and progression of HF with EF.<sup>32–35</sup> The use of MRAs may slow HF progression and prevent or reverse cardiac remodeling and the development of arrhythmias.<sup>30</sup> Although ACE inhibitors block aldosterone, evidence indicates that this effect is only transient.<sup>36</sup> There is little data comparing the efficacy of spironolactone versus eplerenone, but both have proven effective in placebo-controlled trials.<sup>27,29</sup>

The initial and maximum doses of aldosterone antagonists should be adjusted based on renal function (Table 1).<sup>3</sup> Spironolactone, which is chemically similar to progesterone, increases peripheral estradiol formation, potentially leading to adverse events, including gynecomastia or amenorrhea. These adverse events are not seen with eplerenone because it is selective to the aldosterone receptor.<sup>30,31</sup> Furthermore, although ACE inhibitors and aldosterone antagonists are often used concomitantly for patients with HF with EF, concurrent use of these agents can cause life-threatening hyperkalemia.<sup>37</sup> Due to the risk of elevated potassium levels, potassium supplements should be discontinued (or reduced and carefully monitored in those with a history of hypokalemia) when initiating aldosterone antagonist therapy in a patient already receiving an ACE inhibitor. Careful monitoring of potassium levels and renal function should be performed at initiation and closely checked within two to three days and again at seven days after initiation.<sup>3</sup> Patients should subsequently be monitored monthly for the first three months and every three months thereafter. More frequent monitoring may be appropriate for patients who have fluctuating potassium levels, renal function, or fluid status, as well as patients who have had recent changes in their ACE inhibitor/ARB dosing regimens. Additional monitoring parameters include daily measures of blood pressure and weight.<sup>3,27,30</sup>

### DIURETICS

Although no data have shown that they reduce mortality or hospital readmission, diuretics are the only agents that can adequately control the fluid retention associated with HF with EF. Unless contraindicated, diuretics are recommended in all HF with EF patients with fluid retention to improve symptoms. Diuretic use is generally combined with moderate dietary sodium restriction.<sup>3</sup>

Loop diuretics, such as furosemide, are the preferred diuretic agents for most HF with EF patients.<sup>3</sup> Loop diuretics work at the thick ascending limb of the loop of Henle to inhibit sodium and chloride reabsorption.<sup>38</sup> In comparison, thiazide diuretics are less potent and thus have a less significant effect on fluid retention/edema.<sup>39,40</sup> Thiazides work at the renal distal convoluted tubule to inhibit the sodium chloride cotransporter. Due to their antihypertensive effects, thiazide diuretics may be the preferred diuretic agents for HF with EF patients with concurrent hypertension and mild fluid retention.<sup>3,41</sup> Some HF with EF patients may remain volume-overloaded despite the use of maximal loop diuretic therapy.<sup>42</sup> Such loop diuretic resistance may be overcome by intravenous administration of loop diuretics or by the addition of a thiazide diuretic.<sup>3,42</sup>

Adverse effects of diuretics include fluid depletion, hypotension, azotemia, and depletion of sodium, potassium, magnesium, chloride, and calcium. Typical monitoring parameters for these agents include daily weight and blood pressure measurements, and periodic monitoring of renal function. Because loop and thiazide diuretics may increase uric acid, patients utilizing these agents should be monitored for changes in uric acid levels as well as signs and symptoms of gout. The presence of orthopnea and B-type natriuretic peptide levels should be followed daily if possible during inpatient admissions.<sup>43</sup>

Diuretic therapy is initiated at low doses and is titrated up as needed and as tolerated. Adequate treatment is not determined by reaching a set target dose, but rather by looking for an increase in urine output and a 0.5-kg to 1.0-kg decrease in daily weight.<sup>3</sup> These clinical markers should be monitored closely to determine appropriate patient-specific diuretic doses.

### VASODILATORS

Vasodilators have been shown to reduce mortality in patients self-described as African-Americans with NYHA class III–IV HF with EF. They are also recommended to reduce morbidity and mortality in patients with current or prior symptomatic HF with EF who cannot be given an ACE inhibitor or ARB because of drug intolerance, hypotension, or renal insufficiency, unless contraindicated.<sup>6</sup> Both hydralazine and isosorbide dinitrate have vasodilatory effects. Isosorbide dinitrate causes a release of nitric oxide that relaxes vascular smooth muscle, affecting both arteries and veins. In comparison, hydralazine works to selectively relax arterial smooth muscle and may minimize nitrate tolerance.<sup>44,45</sup>

A 1986 trial demonstrated that the one-year mortality rate for the hydralazine and isosorbide dinitrate treatment group was 38% lower than the placebo control group.<sup>9</sup> Furthermore, a study that analyzed hydralazine and isosorbide dinitrate treatment specifically in black patients found a 43% reduction in relative mortality risk and a 33% reduction in first HF with EF hospitalization compared with placebo.<sup>45</sup> Finally, a study that

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evaluated racial differences between white and black patients showed that when comparing hydralazine and isosorbide dinitrate therapy with placebo, mortality benefits were seen only in black patients.<sup>46</sup> These results are thought to be due to the increased incidence of hypertension and decreased levels of plasma norepinephrine and renin typically seen in black patients.

A starting dose of hydralazine 37.5 mg/isosorbide dinitrate 20 mg (available as a combination tablet) three times per day is recommended. When administering hydralazine and isosorbide dinitrate separately, the recommendation is to start with hydralazine 25 mg to 50 mg three or four times per day and isosorbide dinitrate 20 mg to 30 mg three or four times per day. However, the combination tablet will help reduce a patient's pill burden as well as the possible need to cut hydralazine tablets in half depending on the dose. If the medication is tolerated without major side effects for two weeks, the dose can be doubled.<sup>44</sup> The maximum recommended dose is hydralazine 75 mg/isosorbide dinitrate 40 mg three times per day or hydralazine 300 mg daily in divided doses with isosorbide dinitrate 120 mg daily in divided doses.

Adverse effects of hydralazine and isosorbide dinitrate include nausea, fatigue, palpitations, joint pain, and rash. A trial comparing the adverse effects of hydralazine and isosorbide dinitrate to ACE inhibitors found that headaches were seen more often while symptomatic hypotension and cough were seen less often in the vasodilator combination group than in the ACE inhibitor group.<sup>47</sup> The use of phosphodiesterase-5 inhibitors is contraindicated with nitrates due to the increased risk of adverse events such as symptomatic hypotension.<sup>44</sup>

### DIGOXIN

Digoxin has been shown to decrease the rate of HF $\nabla$ EF-related hospitalizations when used in addition to standard of care. Digoxin is a cardiac glycoside that has been used for more than 200 years. It inhibits the sodium-potassium ATPase pump, causing positive inotropy (increasing force and velocity of myocardial contraction) and deactivating neurohormonal effects (decreasing sympathetic and RAAS responses).<sup>48</sup>

Despite extensive use of digoxin, its role and utility in chronic HF have been controversial. However, various studies have elucidated the effects of digoxin on morbidity and mortality in HF $\nabla$ EF patients. HF $\nabla$ EF patients on digoxin who were switched to placebo showed a significant worsening of HF compared with those who continued to receive digoxin therapy (relative risk, 5.9;  $P < 0.001$ ).<sup>49</sup> Symptom severity, as measured by exercise tolerance, showed worsening maximal exercise capacity in patients receiving placebo compared with digoxin therapy (4.5-second change in exercise time;  $P = 0.003$ ).<sup>50</sup> However, digoxin did not demonstrate a mortality benefit in patients with HF $\nabla$ EF or HF $\nabla$ EF.<sup>51</sup> A majority of patients included in these trials were on an ACE inhibitor, a beta blocker, and/or a diuretic at baseline.<sup>49,51</sup>

The many adverse effects of digoxin are generally dose dependent and are far less likely when the drug is used in the recommended dosage range. However, less commonly, cardiac toxicity, including heart block, may be seen in the therapeutic range, especially if patients have hypokalemia, hypomagnesemia, or hypothyroidism. Digoxin toxicity typi-

cally presents with the combination of cardiac effects and dose-dependent central nervous system effects (visual changes, anxiety, dizziness, etc.) or gastrointestinal effects (anorexia, nausea, vomiting, and abdominal pain). Serum trough levels may be monitored to minimize adverse effects. The target trough range for HF $\nabla$ EF patients is 0.4 ng/mL to 0.9 ng/mL.<sup>3</sup> The initial dose of digoxin is typically 0.125 mg to 0.250 mg daily with no need for a loading dose. Patients who are elderly, have poor renal function, or have low lean body mass should start with 0.125 mg daily or every other day.<sup>48</sup>

### IVABRADINE

Ivabradine is a heart-rate-reducing agent approved in the U.S. in 2015 for use in patients with HF $\nabla$ EF. It is indicated in patients with stable, symptomatic, chronic HF with an EF of 35% or less and a resting heart rate greater than 70 beats per minute (bpm).<sup>52,53</sup> It is an inhibitor of the "funny current" or I(f) channel. The I(f) channel controls heart rate through modulation of autonomic neurotransmitters, such as epinephrine. Specific blockade of these channels removes the contribution I(f) has on pacemaker depolarization and thus slows the heart rate.<sup>54</sup>

Ivabradine was evaluated in a randomized, placebo-controlled trial to determine whether lowering a patient's resting heart rate leads to a reduction in cardiovascular death or hospital admission for worsening HF. At baseline, 89% of the patients randomized to the ivabradine group were taking a beta blocker, 79% were taking an ACE inhibitor, 14% were using an ARB, and 22% were taking cardiac glycosides, such as digoxin. The study enrolled patients who had an EF of less than 35% and were in sinus rhythm with a heart rate of 70 bpm or higher. Twenty-four percent of patients in the ivabradine group versus 29% of patients in the placebo group had a primary endpoint event (HR, 0.82; 95% CI, 0.75–0.90;  $P < 0.0001$ ).<sup>55</sup> A subgroup analysis showed that the effects of ivabradine are related to the patient's heart rate. Ivabradine significantly reduced the rates of cardiovascular death and HF hospitalizations in patients taking less than 50% of the guideline-recommended beta-blocker dose. However, no significant difference was seen in the primary endpoint among patients taking 50% or more of the recommended beta-blocker dose.<sup>56</sup>

Ivabradine is typically initiated at 5 mg orally twice daily and is titrated to a target heart rate of 50 bpm to 60 bpm every two weeks. At this time, if the heart rate is greater than 60 bpm, the dose of ivabradine should be increased by 2.5 mg per dose. The maximum dose is 7.5 mg orally twice daily. In comparison, if the heart rate is less than 50 bpm or a patient presents with symptomatic bradycardia, the dose should be decreased by 2.5 mg per dose and discontinued if necessary.<sup>53</sup>

A significantly higher rate of symptomatic bradycardia, atrial fibrillation, and visual changes occurred in patients receiving ivabradine compared with placebo.<sup>55</sup> Due to these adverse events, this agent should be avoided in patients with resting heart rates less than 60 bpm, low blood pressure, decompensated HF $\nabla$ EF, and cardiac conditions, including sick sinus syndrome, sinoatrial block, or third-degree heart block. Due to its hepatic metabolism, ivabradine should be avoided in patients with severe hepatic impairment and with concomitant use of potent cytochrome P450 3A4 inhibitors.<sup>53</sup>

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The 2016 focused update to the 2013 ACCF/AHA guidelines recommends ivabradine use in patients with symptomatic, stable, chronic NYHA class II–III HF $\neq$ EF with an EF of 35% or less who are in sinus rhythm and have a resting heart rate of at least 70 bpm. It is important to titrate beta blockers to their maximally tolerated dose prior to initiation of ivabradine for additional control.<sup>6</sup>

Many unanswered questions remain about this medication that need to be studied to determine a more specific role in therapy. For example, what is the role of digoxin in comparison with ivabradine for heart rate control? Further studies are necessary to determine the full benefit of this agent.

### SACUBITRIL/VALSARTAN

ARNIs are a new class of medications that may have a growing role in HF treatment. Sacubitril/valsartan is a novel therapy approved in July 2015 to reduce the risk of cardiovascular death and hospitalization for patients with HF $\neq$ EF (NYHA class II–III). Sacubitril/valsartan consists of the neprilysin inhibitor sacubitril and the ARB valsartan. Neprilysin is a neutral endopeptidase that metabolizes endogenous vasoactive peptides, including natriuretic peptides, bradykinin, and substance P into their inactive metabolites. Inhibition of neprilysin increases the levels of these substances and decreases vasoconstriction, sodium retention, abnormal growth, and remodeling.<sup>5</sup> However, angiotensin II is also a substrate of neprilysin. Thus, the addition of an ARB to the neprilysin inhibitor is necessary to prevent activation of the RAAS.

Previous studies, such as OVERTURE, investigated the combination of a neprilysin inhibitor with an ACE inhibitor.<sup>57</sup> Although the combination was shown to reduce mortality and hospitalization in chronic HF, it was not more effective than ACE inhibition alone and was associated with a higher rate of angioedema. Alternatively, PARADIGM-HF investigated the combination of the neprilysin inhibitor sacubitril and the ARB valsartan. PARADIGM-HF aimed to study the long-term effects of sacubitril/valsartan 200 mg twice daily on mortality and hospitalization compared with enalapril 10 mg twice daily in patients with HF $\neq$ EF. To be considered for trial inclusion, patients were required to tolerate a stable dose of a beta blocker and an ACE inhibitor or ARB equivalent of at least 10 mg of enalapril daily for at least four weeks prior to trial screening. At baseline, of the 4,187 patients in the sacubitril/valsartan group, 78% were using an ACE inhibitor, 22.2% were on ARBs, 93.1% utilized a beta blocker, and 54.2% were taking an MRA. The study was stopped early (after the third interim analysis) due to a clear statistical and clinical advantage for sacubitril/valsartan; median follow-up was 27 months. The HR for sacubitril/valsartan for composite death from cardiovascular causes or first hospitalization for worsening HF was 0.80 (95% CI, 0.73–0.87;  $P < 0.001$ ). Furthermore, when comparing sacubitril/valsartan with enalapril, the absolute risk reductions for death from cardiovascular cause and first hospitalization for worsening HF were found to be 3.2% ( $P < 0.001$ ) and 2.8% ( $P < 0.001$ ), respectively.<sup>5</sup> The total daily strength of the combination product used in the trial offered bioavailability similar to 320 mg valsartan. Although this is the desired target dose of valsartan according to the ACCF/AHA heart failure guidelines, the comparator (enalapril) was not pushed to its desired target

dose. While less than the desired target dose, the studied dose of enalapril in PARADIGM-HF is reflective of the doses used in previous trials, such as CONSENSUS and SOLVD.<sup>7,8</sup> Therefore, this new ARB and neprilysin inhibitor combination offers an additional option for patients who have optimized current guideline-supported therapies.

Special consideration should be given when determining the appropriate dose of sacubitril/valsartan. Clinical trials, such as PARADIGM-HF, studied Entresto 200 mg, which includes sacubitril 97 mg and valsartan 103 mg. Available preparations now include a range of sacubitril and valsartan strengths, including the dose studied in PARADIGM-HF, as well as doses that were not studied in the trial, including sacubitril 24 mg/valsartan 26 mg and sacubitril 49 mg/valsartan 51 mg. The valsartan component in the combination product is more bioavailable than valsartan in other marketed formulations. Valsartan strengths of 26 mg, 51 mg, and 103 mg in sacubitril/valsartan offer a similar bioavailability to valsartan 40 mg, 80 mg, and 160 mg, respectively, in other marketed formulations.<sup>58</sup>

During the single-blind run-in period with enalapril and sacubitril/valsartan in PARADIGM-HF, 12.0% of the patients withdrew because of an adverse event.<sup>5</sup> Adverse reactions to ARNIs include hypotension, hyperkalemia, increased serum creatinine, angioedema, cough, and renal failure. Although there were fewer incidences of angioedema in clinical trials with ARNIs than with the combined ACE and neprilysin inhibition, PARADIGM-HF showed that the risk of angioedema was still a concern.<sup>5</sup> Angioedema occurred in 19 patients in the sacubitril/valsartan group and 10 patients in the enalapril group ( $P = 0.13$ ).<sup>5</sup> However, only 5% of the patients enrolled were African-American. Because African-Americans have a relatively higher risk of angioedema with ACE inhibitors and ARBs, the optimal agent for this high-risk population remains unclear. Monitoring parameters for ARNIs include baseline and periodic serum potassium, renal function, and blood pressure. ARNIs should be used with caution in patients with aortic/mitral stenosis, renal artery stenosis, or renal/hepatic impairment. Medications that work on the RAAS system (including ARNIs) should be discontinued as soon as pregnancy is detected because these agents can cause injury or death to the developing fetus.

The 2016 ACCF/AHA/HFSA focused update recommends use of ARNIs in patients with chronic symptomatic HF $\neq$ EF NYHA class II or III who can tolerate an ACE inhibitor or an ARB to further reduce morbidity and mortality in conjunction with beta-blocker therapy. These guidelines caution not to administer ARNIs with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor due to the increased risk of angioedema. ARNIs should also not be administered in patients with a history of angioedema.<sup>6</sup> In contrast, the 2016 European Society of Cardiology guidelines recommend the use of an MRA prior to initiating an ARNI.<sup>4</sup>

### CONCLUSION

Beta blockers and ACE inhibitors have been proven to reduce morbidity and mortality in a wide range of HF $\neq$ EF patients.<sup>7,8,23,25</sup> These proven benefits warrant the use of these agents in all patients with HF. MRAs such as spironolactone and eplerenone have also been shown to reduce morbidity and mortality in

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addition to ACE inhibitors and beta blockers in patients with HF $\nabla$ EF, depending on the NYHA class and EF. Therapy should always be individualized, but one of these agents can be added to base therapy for additional benefits.<sup>27</sup> Vasodilators show morbidity and mortality benefit in African-American patients in specific situations and can be added to therapy.<sup>45,46</sup>

To help reduce morbidity in patients, additional agents may be added for symptomatic relief. In patients with signs and symptoms of fluid overload, diuretics should be used to help mobilize and excrete the excess fluid. Specifically, loop diuretics are seen as the first-choice agents, but thiazides may be added to overcome loop resistance.<sup>6,42</sup> Digoxin may be added for symptom relief and to decrease morbidity. Though it does not show mortality reduction, it has demonstrated utility in decreasing hospitalizations for worsening HF $\nabla$ EF.<sup>50,51</sup>

Ivabradine may be added to treatment in patients on beta blockers who have persistently elevated heart rates or who cannot tolerate beta blockers. The addition of ivabradine will further reduce morbidity, mortality, and hospitalizations in these patients, because increased rates of cardiovascular death, hospitalization for HF and myocardial infarction, and coronary revascularization have been reported in patients with heart rates greater than 70 bpm.<sup>52,55</sup> Thus, ivabradine should be considered add-on therapy in select patients with persistently elevated heart rates despite beta-blocker therapy.<sup>56</sup>

ARB and neprilysin inhibitor combination products (such as sacubitril/valsartan) offer a new option for patients. These agents may have a role in patients who remain symptomatic despite reaching maximum doses of ACE inhibitors/ARBs and beta blockers.

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