Heart failure (HF) affects an estimated 26 million people worldwide. In the United States, 5.6 million individuals are estimated to have the condition, resulting in nearly $30 billion in health care-associated costs. In westernized countries, acute decompensated HF is the leading cause for hospital admissions and is associated with a three-month post-discharge mortality rate of 7% to 11%. The risk for this disease increases as a person ages, with an estimated 8.4% prevalence in those 75 years of age and older, compared with 0.7% of the population 45 to 54 years of age. With the geriatric population expected to double to more than 80 million by 2050, HF can be expected to have an increasingly substantial impact on the U.S. health care system.

In HF, the heart’s ventricles ultimately lose their ability to effectively fill with or pump blood, which results in increased fluid retention, dyspnea, fatigue, and organ damage from hypoperfusion. Additional complications such as hyponatremia, liver or kidney damage, and arrhythmias may also develop. HF symptoms can make it difficult to perform everyday tasks, such as walking several blocks or cleaning the house, severely disrupting a patient’s quality of life.

HF is categorized into two subsets based upon a patient’s left ventricular ejection fraction (LVEF). Heart failure with reduced ejection fraction (HFrEF) is generally described as an LVEF of less than 40%, and heart failure with a preserved ejection fraction (HFpEF) is defined as an LVEF greater than 50%. Following diagnosis, patients are also grouped into one of four classes based upon their symptom status (Table 1), and this categorization is used to determine a patient’s eligibility for specific drug therapies.

### New Heart Failure Medications Aim To Fill Significant Gaps in Treatment

Troy Kish, PharmD, BCPS

The current approach to treating patients with HF involves using a combination of medications with complementary mechanisms of action to improve the patient’s cardiac function. Most agents used in both chronic and acute care settings are generic medications with which practitioners have extensive experience. Medication classes commonly used include beta blockers, angiotensin-converting enzyme inhibitors, angiotensin-receptor antagonists, aldosterone antagonists, and loop diuretics.

Despite the number of medications already available, patients with HF often have frequent disease exacerbations, reduced quality of life, and increased mortality, highlighting the need for new treatment approaches. Specialists note several areas of unmet need, such as:

- Therapies that specifically target HFpEF
- Therapies that can be used safely in patients with multiple medical comorbidities
- Therapies that reverse cardiac damage rather than slow disease progression
- Medications used in the setting of acute HF exacerbation

With so many opportunities and potential targets, there is a robust pipeline of potential new agents for the treatment of HF. We will discuss four therapies—in alphabetical order—that aim to enter the market over the next several years (Table 2).

### EMERGING THERAPIES FOR HF

#### CXL-1427

Bristol-Myers Squibb’s candidate HF medication CXL-1427 is aimed at treating acutely decompensated patients. CXL-1427 acts as a donor of nitric oxide to help increase intracellular cyclic guanosine monophosphate (cGMP), leading to the cascade of beneficial effects such as natriuresis, vasodilation, and diuresis. A phase 1 dose-escalation study in 70 healthy patients receiving a 48-hour infusion of CXL-1427 showed the medication to be well tolerated, with headache and nausea being the most common adverse effects at doses up to 10 mcg/kg per minute. Clinical data are limited because results from a dose-finding phase 2a trial have not been published, and a phase 2b efficacy trial known as STANDUP-AHF is currently enrolling participants, with an anticipated completion date of spring 2019.

This market has been notoriously difficult to enter, as demonstrated by the long-standing unmet need for new therapies. Recently both Novartis and Cardiorentis had agents fail to gain Food and Drug Administration (FDA) approval due to

### Table 1 Classes and Stages of Heart Failure

<table>
<thead>
<tr>
<th>Class of Heart Failure According To the New York Heart Association®</th>
<th>Stages of Heart Failure According to the American College of Cardiology and American Heart Association®</th>
</tr>
</thead>
<tbody>
<tr>
<td>I–No limitation of physical activity. Ordinary physical activity doesn’t cause undue fatigue, palpitation, or dyspnea.</td>
<td>A–At risk for heart failure but without structural changes or symptoms</td>
</tr>
<tr>
<td>II–Ordinary physical activity results in fatigue, palpitation, or dyspnea.</td>
<td>B–Structural heart disease but without signs or symptoms of heart failure</td>
</tr>
<tr>
<td>III–Marked limitation of physical activity. Comfortable at rest but less than ordinary activity leads to fatigue, palpitation, or dyspnea.</td>
<td>C–Structural heart disease with current or prior symptoms of heart failure</td>
</tr>
<tr>
<td>IV–Symptoms of heart failure at rest. Any physical activity increases discomfort.</td>
<td>D–Refactory heart failure including specialized interventions</td>
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lack of long-term outcome improvements, which sets the bar high for the performance of CXL-1427. Analysts have reservations about the drug’s ability to obtain FDA approval because of regulators’ expectation that new agents must demonstrate improved mortality beyond the acute-care time frame, and this may be difficult for medications given for only 24 to 48 hours. Contingent on successful phase 3 trials and FDA approval, CXL-1427 would launch in 2024 as an adjunct therapy to loop diuretics in the treatment of acute decompensated heart failure episodes.

### Omecamtiv Mecarbil

Cytokinetics developed omecamtiv mecarbil (OM), a novel, small-molecule, direct activator of cardiac adenosine triphosphatase, for use in HFrEF patients following an acute exacerbation. Use of OM results in increased LV ejection time and stroke volume while not impacting a patient’s systolic blood pressure. OM also has the beneficial effect of reducing the patient’s heart rate.

The ATOMIC-AHF phase 2 trial, completed in 2013, evaluated the dosing, efficacy, and safety of a 48-hour infusion of OM in 606 patients with an acute HF exacerbation and an LVEF of 40% or less. Overall, no statistical difference was seen in the primary outcome, improvement in dyspnea, when comparing OM to placebo; however, when evaluating patients receiving the highest dose of OM (target plasma concentration, 310 ng/mL; plasma concentration achieved, 425 ng/mL), the dyspnea response rate was 51% versus 37% (P < 0.003) compared with placebo. Observed adverse effects were hypotension, hypokalemia, acute renal failure, and cardiac failure, but these were all reported at a rate similar to placebo.

The phase 2 COSMIC-HF trial evaluated patients receiving oral OM in doses of 25 mg or 50 mg twice daily for up to 20 weeks. All endpoints, such as improved stroke volume and systolic ejection time, as well as reductions in heart rate and N-terminal pro-brain natriuretic peptide (BNP) levels, were significantly improved in the 50-mg OM group compared with placebo (all P < 0.05). Clinical outcomes were not evaluated in this trial.

Cytokinetics has partnered with Amgen to continue development of OM and enrollment for the phase 3 GALACTIC-HF trial is under way. This trial will compare OM titrated to 50 mg orally twice daily with placebo in patients 18 to 85 years of age with New York Heart Association (NYHA) class II–IV symptoms and an LVEF of 35% or less who are admitted for an HF exacerbation, hospitalized with a prior HF exacerbation, or had an urgent HF admission within the last year. The primary endpoints are cardiovascular (CV) death or readmission for HF. An anticipated 8,000 participants are expected to be evaluated and followed for up to 208 weeks, with an anticipated trial completion date of January 2021.

While OM has the potential to fill a largely unmet clinical need, the results of Novartis’ PIONEER-HF trial evaluating sacubitril/valsartan (Entresto) in a similar population are expected to be published ahead of GALACTIC-HF. It is important to note that the endpoints for these trials differ, with PIONEER-HF evaluating only N-terminal pro-BNP levels as well as the incidences of hyperkalemia, symptomatic hypotension, and angioedema. This will give OM an advantage if it can show reduced CV mortality and rehospitalization.

Pending successful results in the phase 3 trial and approval from the FDA, OM is expected to launch in the United States in 2022. Introduction of this medication would represent a unique approach to patient therapy because it will be initiated while HFrEF patients are still admitted to the hospital as a way to improve their transition back to outpatient status.

### RT-100

Renova Therapeutics is developing a novel approach to treating HF patients through gene transfer therapy. Its leading drug candidate, RT-100, targets human adenylyl cyclase type 6 (AC6), a protein downregulated in many HF patients. This one-time therapy is administered via cardiac catheterization and delivered to the site by an adenovirus type 5

### Table 2  New Therapies in Development for the Treatment of Heart Failure

<table>
<thead>
<tr>
<th>Drug Developer(s)</th>
<th>Mechanism Of Action</th>
<th>Targeted Indication/Population</th>
<th>Route and Dose</th>
<th>Expected Price Strategy</th>
<th>Estimated AWP/Year</th>
<th>Anticipated U.S. Launch</th>
</tr>
</thead>
<tbody>
<tr>
<td>CXL-1427, Bristol-Myers Squibb</td>
<td>Donor of nitric oxide</td>
<td>HFrEF patients experiencing acute decompensation</td>
<td>Continuous 48-hour infusion (final dosing, duration TBD)</td>
<td>Estimated 10% premium over nesiritide (Natrecor, Scies, Inc.)</td>
<td>$2,500/course of therapy</td>
<td>2024</td>
</tr>
<tr>
<td>Omecamtiv mecarbil, Amgen/Cytokinetics</td>
<td>Direct activation of cardiac myosin</td>
<td>NYHA class II–IV HFrEF patients with post-acute decompensation</td>
<td>50 mg orally twice daily</td>
<td>Estimated 10% more than ivabradine (Corlanor, Amgen)</td>
<td>$6,800&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2022</td>
</tr>
<tr>
<td>RT-100, Renova Therapeutics</td>
<td>Human adenylyl cyclase type 6 gene therapy</td>
<td>Patients with chronic HFrEF</td>
<td>Single dose given via intracoronary injection (final dose TBD)</td>
<td>Priced lower than existing gene therapies but is noncurative</td>
<td>$200,000</td>
<td>2024</td>
</tr>
<tr>
<td>Vericiguat, Bayer/Merck</td>
<td>Soluble guanylyl cyclase activator</td>
<td>NYHA class II–IV HFrEF patients with history of recent decompensation</td>
<td>10 mg orally daily</td>
<td>Estimated 10% more than ivabradine</td>
<td>$6,800&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2021</td>
</tr>
</tbody>
</table>

<sup>a</sup> Calculated using AWP of $515 per month for ivabradine.
vector. Upon delivery, AC6 enhances the conversion of ATP to cyclic adenosine monophosphate (cAMP) and improves the ability of cardiac cells to mediate the flow of calcium, which is crucial for both contraction and relaxation of the ventricles.15

A successful phase 2 study involving 56 patients with chronic HFrEF demonstrated significantly improved LVEF at four weeks in RT-100–treated patients when compared with baseline (36.3% versus 29.7%; P < 0.004), but at the 12-week evaluation RT-100 was unable to maintain a statistical difference (34.2% versus 29.7%; P = 0.16). As a secondary endpoint, rates of HF admissions were 9.5% in the RT-100 group and 28.6% in the placebo group (relative risk, 0.33; 95% confidence interval, 0.09–1.36; P = 0.10). RT-100 was noted to be well tolerated, with an adverse event profile similar to placebo.16 These results have paved the way for a phase 3 trial set to begin enrollment by the end of 2017. The primary endpoint will be reduction in both first-time and repeat hospitalizations over 12 months.17 Pending FDA approval, RT-100 would be expected to enter the U.S. market in 2024 and would be positioned to be the first gene therapy on the market for HF.9

**Verciguit**

Verciguit, a novel agent produced by Bayer Healthcare and Merck, is an oral, soluble guanylyl cyclase activator that targets patients with HFrEF and worsening disease. Through activation of guanylyl cyclase, intracellular levels of cGMP are increased, leading to natriuresis, diuresis, and vasodilation.9

The phase 3 VICTORIA trial will enroll 4,800 patients with an LVEF of less than 45%, NYHA class II–IV disease, and a hospitalization in the previous six months. The primary endpoint is a composite of CV death or hospitalization for HF. The expected completion of this trial is January 2020.18 Results will be highly anticipated because Bayer and Merck are moving forward despite the findings of the phase 2 SOCRATES-Reduced trial. This study showed verigicuit had no impact on N-terminal pro-BNP, CV death, or positive changes in left ventricular function; however, secondary analysis of the results suggested a positive relationship between increasing dose and improved N-terminal pro-BNP reduction.19 Thus far in published literature, verigicuit has been well tolerated, with hypotension and syncope being the most commonly reported adverse effects.

Following FDA approval, verigicuit would likely enter the U.S. market in 2021. This agent would be added to standard therapy in patients who have recently experienced a disease exacerbation.9

**CONCLUSION**

Looking further down the development pipeline, there are dozens of medications in various phases of research targeting both chronic and acute heart failure patients. This reflects the large unmet needs of this population as well as the financial implications that come with this condition. Over the coming decade, we can expect the therapeutic and market aspects of heart failure to expand substantially.

**REFERENCES**


