New Management Strategies in Heart Failure
Anjali Tiku Owens, Susan C. Brozena, Mariell Jessup

Abstract: Despite >100 clinical trials, only 2 new drugs had been approved by the US Food and Drug Administration for the treatment of chronic heart failure in more than a decade: the aldosterone antagonist eplerenone in 2003 and a fixed dose combination of hydralazine–isosorbide dinitrate in 2005. In contrast, 2015 has witnessed the Food and Drug Administration approval of 2 new drugs, both for the treatment of chronic heart failure with reduced ejection fraction: ivabradine and another combination drug, sacubitril/valsartan or LCZ696. Seemingly overnight, a range of therapeutic possibilities, evoking new physiological mechanisms, promise great hope for a disease that often carries a prognosis worse than many forms of cancer. Importantly, the newly available therapies represent a culmination of basic and translational research that actually spans many decades. This review will summarize newer drugs currently being used in the treatment of heart failure, as well as newer strategies increasingly explored for their utility during the stages of the heart failure syndrome. (Circ Res. 2016;118:480-495. DOI: 10.1161/CIRCRESAHA.115.306567.)

Key Words: cardiomyopathies ■ drug combinations ■ heart failure ■ pharmacology ■ United States Food and Drug Administration

Between 2001 and 2012, 154 clinical trials in heart failure (HF) involving 162,725 patients were undertaken; the majority of which investigated the treatment for chronic HF with reduced ejection fraction (HFrEF).1 Enrollment rates did not significantly change over time, but those trials meeting their primary end point decreased during the same time period. As a result, until 2015, only 2 new drugs had been approved by the US Food and Drug Administration for the treatment of HFrEF in more than a decade: the aldosterone antagonist eplerenone in 2003 and a fixed dose combination of hydralazine–isosorbide dinitrate in 2005. In contrast, 2015 has witnessed the Food and Drug Administration approval of 2 new drugs, both for the treatment of chronic HFrEF: ivabradine and another combination drug, sacubitril/valsartan or LCZ696 (Table 1). Seemingly overnight, a range of therapeutic possibilities, evoking new physiological mechanisms, promise great hope for a disease that often carries a prognosis worse than many forms of cancer. Importantly, the newly available therapies represent an extension of a timeline2 predicated on basic and translational research. This review will summarize newer drugs currently being used in the treatment of HF, as well as newer strategies increasingly explored for their utility during the stages of the HF syndrome.

Pharmacotherapy: Emerging Drugs and Concepts

Sacubitril/Valsartan or LCZ696

LCZ696 is a first-in-class angiotensin receptor neprilysin inhibitor (NEPi; ARNi). Although a NEPi was first synthesized in 1980,3,4 the initial clinical use of these agents as a single drug class in hypertension was disappointing. However, when NEPi was combined with an angiotensin-converting enzyme inhibitor, or later, with an angiotensin receptor blocker (ARB), the dual actions of the drugs together were more effective than either alone.5 The development of angioedema in many patients given a combination of NEPi and angiotensin-converting enzyme inhibitor facilitated the development of the ARNI class.6

Circulating natriuretic peptides, which include atrial natriuretic peptide, B-type natriuretic peptide (BNP), and urodilatin, are secreted by the heart, vasculature, kidney, and central nervous system in response to increased cardiac-wall stress and other stimuli, resulting in a potent natriuretic and vasodilatory effect. In addition, the natriuretic peptides inhibit the renin–angiotensin–aldosterone system, reduce sympathetic drive, and have antiproliferative and anti hypertrophic effects as well.7 The interactive role of natriuretic peptides to influence the development of myocardial fibrosis is being clarified.8 Natriuretic peptides are cleared through 2 mechanisms: degradation of the enzyme (neprilysin) and a natriuretic peptide receptor–mediated clearance; NEPi results in an increased concentration of natriuretic peptides. Drugs that inhibit the renin–angiotensin–aldosterone system have been foundational to cardiovascular drug therapy for almost 3 decades; the beneficial effects of renin–angiotensin–aldosterone system inhibition seem to be augmented by the enhancement of natriuretic peptide activity (Figure 1).

The first randomized clinical trial of LCZ696 in HF was in 301 HF with preserved ejection fraction (HFpEF)

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patients, the Prospective Comparison of ARNI With ARB on Management of Heart Failure With Preserved Ejection Fraction (PARAMOUNT) trial. The primary end point, plasma N-terminal pro-BNP (NT-proBNP), was significantly lower at the end of 12 weeks in the LCZ696 group compared with the valsartan (an ARB) patients. By 36 weeks, the patients in the LCZ696 arm had improved New York Heart Association (NYHA) symptoms and smaller left atrial volumes—used as a surrogate for ventricular filling pressures—in comparison with the ARB-treated patients. A larger HFpEF trial is now underway, the Prospective Comparison of LCZ696 With ARB Global Outcome in HF With Preserved Ejection Fraction (PARAGON) trial. These encouraging preliminary findings were followed by a trial in HFrEF.

In a Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial, LCZ696 was compared with an enalapril-based, guideline-directed regimen in 8442 symptomatic patients with HFpEF. LCZ696, compared with enalapril, significantly and remarkably reduced the risks of death from any cause, from cardiovascular causes, and the risk of hospitalization for HF. Patients’ quality of life, as measured by the Kansas City Cardiomyopathy Questionnaire, was significantly improved as well. Subsequent publications from this same trial revealed that LCZ696 was superior to enalapril in reducing sudden cardiac death and preventing the clinical progression of HF in survivors.

The results of the PARADIGM-HF trial generated a wave of enthusiasm for the promise of a new drug class for patients with HFpEF; discussions about the potential to change the guidelines quickly followed. Translating the remarkable statistical results of the trial into a guideline recommendation, however, has triggered some concerns. The trial was stopped early, according to the prespecified metrics of the trial design, after a median follow-up of 27 months, because of the overwhelming benefit seen with LCZ696. Thus, some have voiced concerns about the durability of the drug’s effect over many more years and potential adverse effects of long-term use of LCZ696. In addition, patients enrolled in the trial had a several week run-in period to demonstrate their ability to tolerate 10 mg of both LCZ696 and enalapril twice daily. LCZ696 was given initially at a dose of 100 mg twice daily, which was increased to 200 mg twice daily. The ARB component of the 200-mg dose of LCZ696 is equivalent to 160 mg of valsartan. The doses of both the angiotensin-converting enzyme inhibitor and the ARB in the ARNi are higher than many HFpEF patients may tolerate, although are clearly target dosages listed in most HF guidelines. Guideline-writing committees will need to weigh the obvious potential benefit of the drug against the need to carefully describe the typical patient who might be considered for initiation. Finally, this considerable challenge to the long-standing algorithm of care for the patient with HFpEF will be further complicated by the cost of the drug in the United States. Clinicians are already reporting a high frequency of drug denials from payors.

Nevertheless, the ARNi class has sparked considerable excitement as a strategy in other cardiovascular disorders, including hypertension. LCZ696 has been shown to attenuate
myocardial fibrosis and remodeling after a myocardial infarction in an animal model\textsuperscript{16} and to preserve renal function better than an ARB alone in patients with HFpEF\textsuperscript{17}. The Food and Drug Administration approved LCZ696 as a treatment for HFrEF on July 7, 2015.

**Ivabradine**

In April of the same year, ivabradine was approved in the United States to reduce the risk of hospitalization in stable HFrEF patients with a heart rate >70 bpm despite optimal use of $\beta$-blocking agents. The drug has been available in Europe since 2005. Ivabradine is a specific inhibitor of the $I_f$ current in the sinoatrial node, and at concentrations used clinically has no other apparent action on the myocardium or vascular system. Mechanistically, it is used exclusively to reduce the heart rate in patients; an intensified interest in the prognostic implications of heart rate reduction has resumed\textsuperscript{18–20}.

In the Systolic Heart Failure Treatment With the $I_f$ Inhibitor Ivabradine Trial (SHIFT) study, 6558 patients with HFrEF in sinus rhythm with a heart rate >70 bpm were randomized to evidence-based treatment with or without ivabradine\textsuperscript{21}. The primary end point was the composite of cardiovascular death or hospital admission for worsening HF. There was a significant, 18% decrease in risk of cardiovascular death or admission with ivabradine compared with placebo, primarily fueled by the salutary effect on hospitalization events. The authors suggested that the SHIFT trial was a test of the effect of isolated heart rate reduction on a HFrEF population, as

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<td>Treatment Group, n=3241</td>
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<td>Hazard Ratio</td>
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<td>Hazard Ratio</td>
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CV indicates cardiovascular; HF, heart failure; PARADIGM, Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity; and SHIFT, Systolic Heart Failure Treatment With the $I_f$ Inhibitor Ivabradine.
treatment with ivabradine during the trial averaged a reduction of 15 bpm from the baseline heart rate of 80 bpm. Moreover, patients with higher heart rates seemed to benefit more from ivabradine. Skeptics worried that the same magnitude of effect would have been seen if the patients had been given a higher dose of β-blockade. A subsequent publication with additional analyses argued that the magnitude of heart rate reduction by ivabradine beyond what was achieved by a β-blocker, rather than background β-blocker dose, primarily determined the subsequent outcome.22

Interestingly, in a previous study in patients with coronary artery disease and low left ventricular ejection fraction (LVEF), ivabradine did not confer a clinical benefit,23 but the subgroup with a heart rate of ≥70 bpm at baseline despite guideline-based therapy had improved outcomes. Accordingly, the Study Assessing the Morbidity–Mortality Benefits of the I, Inhibitor Ivabradine in Patients With Coronary Artery Disease (SIGNIFY) trial was done, involving patients with stable coronary artery disease and no HF symptoms; patients with LVEF <40% were excluded.24 The primary end point was a composite of death from cardiovascular causes or nonfatal myocardial infarction. The SIGNIFY trial showed no clinical benefit with ivabradine in this patient population. Thus, the use of the drug at present should be confined to the specific HFrEF patients with higher heart rates despite maximally tolerated β-blocker therapy.

Aliskiren

Given the enormous benefit of more proximal inhibition of the renin–angiotensin–aldosterone system in the HF syndrome and the known compensatory increase in renin as a consequence of these agents, the development of direct renin inhibitors was a logical step. Aliskiren is an orally active direct renin inhibitor, approved for use in hypertension in the United States in March of 2007. Previous trials in patients with HF suggested a favorable hemodynamic response to the drug: an observed increase in renal blood flow in normal subjects was especially noteworthy.25 A subsequent trial in patients with symptomatic HF showed that aliskiren decreased BNP levels, plasma renin, and urinary aldosterone more than placebo.26

The Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT) study was, therefore, designed to evaluate the effect of aliskiren or placebo, added to standard medical therapy, on hospitalized patients with HFrEF.27 The primary end point was cardiovascular death or HF rehospitalization at 6 months. Studied in >1600 patients, aliskiren had no significant effect on the primary composite end point or on any clinical end point ≤12 months of follow-up. Not unexpectedly, patients who received aliskiren had more hyperkalemia, hypotension, and renal impairment.

A provocative, prespecified subgroup analysis of ASTRONAUT revealed a variable outcome in the trial dependent on baseline diabetic status. The risk of all-cause mortality with aliskiren significantly decreased at 12 months in nondiabetic patients; these same patients experienced less adverse events from aliskiren.28 A similar adverse event profile of aliskiren in diabetic patients was seen in another trial in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both.29 These latter investigators concluded that there was no role for aliskiren in patients with type 2 diabetes mellitus; this caveat is likely applicable to the majority of patients with HF and diabetes mellitus as well.

Iron Therapy

It has been recognized for many years that patients with chronic HF are frequently anemic; iron deficiency and disordered iron homeostasis are often found to be important contributors to the anemia.30,31 The presence and degree of anemia have functional correlates in patients with symptomatic HF and have been shown to be a determinant of prognosis. Correcting anemia with synthetic erythropoietin was shown to be an ineffective method to improve outcomes for patients with HFrEF in the Reduction of Events By Darbepoetin Alfa in Heart Failure (RED-HF) trial.32 The Ferric Carboxymaltose Assessment in Patients With Iron Deficiency and Chronic Heart Failure (FAIR-HF) study randomized 459 ambulatory HFrEF patients with iron deficiency (with or without anemia) to placebo or intravenous iron formulated as ferric carboxymaltose. The treatment with intravenous iron improved symptoms, functional capacity, and quality of life and was well tolerated.33 A later analysis of these same patients showed that renal function was enhanced with iron as well.34

Despite these persuasive findings, routine screening for iron deficiency did not become a standard practice in most HF programs. Accordingly, the Ferric Carboxymaltose Evaluation on Performance in Patients With Iron Deficiency in Combination With Chronic Heart Failure (CONFIRM-HF) trial was undertaken to address the sustainability of iron’s beneficial effects.35 The study enrolled 304 ambulatory, symptomatic HFrEF patients with elevated natriuretic peptides and iron deficiency to intravenous ferric carboxymaltose or placebo, in addition to evidenced-based therapy; patients were followed up for 1 year. The iron therapy resulted in a sustained improvement in functional capacity, symptoms, and quality of life. Importantly, a post hoc analysis showed a significant risk reduction of hospitalization for worsening HF in the iron group. Taken together, these data provide a compelling argument for the inclusion of regular screening for iron deficiency in all patients with HFrEF. Unresolved issues surrounding the role of iron supplementation include (1) the optimal formulation of the iron to be used, as both trials referred to above used intravenous ferric carboxymaltose, and (2) whether iron administered orally can be equally effective. The ongoing trial Oral Iron Repletion Effects on Oxygen Uptake in Heart Failure (IRONOUT) is underway in the National Heart, Lung, and Blood Institute Heart Failure Network to explore the role of oral iron polysaccharide compared with placebo on functional capacity in patients with HFrEF (Table 2).

Phosphodiesterase Type 5 Inhibitor

The phosphodiesterase type 5 (PDE5) inhibitors have become one of the principle classes of therapy for patients with pulmonary arterial hypertension.36 Because left HF so commonly leads to pulmonary hypertension—World Health Organization group 2 pulmonary hypertension—it seemed appropriate to evaluate the effect of the PDE5 inhibitors in patients with either HFrEF or HfP EF. Kass37 has elegantly summarized the many
potential mechanisms whereby the PDE5 inhibitors might improve cardiovascular function in HF. PDE5 plays an important role in the hydrolysis of cyclic GMP; through its primary signaling kinase, protein kinase G, cyclic GMP can modify stress remodeling in the heart and other vascular beds. As a result, PDE5 inhibition has been shown to restrain cardiac pressure and volume overload, ischemic injury, and cardiotoxicity.

In patients with HF being considered for cardiac transplant or the implantation of left ventricular assist devices (VADs), it becomes critical to reduce elevated pulmonary vascular resistance, irreversible pulmonary hypertension leads to right ventricular failure after surgery in the absence of such efforts. The PDE5 inhibitors, primarily sildenafil, are increasingly used to lower abnormal pulmonary pressures in this clinical scenario. Patients with HFpEF have also been shown to have a steep increase in pulmonary pressures with exertion. Thus, the Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure With Preserved Ejection Fraction (RELAX) trial was developed to compare sildenafil with placebo on exercise capacity in patients with HFpEF. The investigators enrolled 216 stable outpatients with an LVEF ≥50%, elevated NT-proBNP or measured filling pressures, and reduced exercise capacity. Despite a strong physiological rationale, the PDE5 inhibitor had no effect on any aspect of exercise capacity, clinical status, quality of life, diastolic function parameters, or pulmonary pressures. Biomarkers increased more with sildenafil, and renal function worsened more than placebo. Further investigation into the cardiovascular adverse effects observed in the trial revealed a negative inotropic action of sildenafil. A trial of PDE5 inhibition in HFrEF had been planned but has been delayed for unclear reasons.

**Glucagon-Like Peptide-1 Receptor Agonists**

A second class of drugs, glucagon-like peptide-1 receptor (GLP-1) agonists, currently used for diabetes mellitus, has also been repurposed for HF. The effect of diabetes mellitus on the outcome and pathophysiology of HF is an area of great investigative interest. GLP-1 is a naturally occurring incretin peptide released from the intestine that enhances cellular glucose uptake by stimulating insulin secretion and enhancing insulin
GLP-1 receptors have been identified in the heart, kidneys, and blood vessels; GLP-1 stimulation has a salutary effect on endothelial function, sodium excretion, recovery from ischemic injury, and myocardial function in animals. It has been argued that GLP-1 agonists have the potential to augment cardiac function by providing fuel for the energy-starved failing heart. Accordingly, the Functional Impact of GLP-1 for Heart Failure Treatment (FIGHT) study was designed by the National Heart, Lung, and Blood Institute Heart Failure Network to explore the use of a GLP-1 agonist or placebo in high-risk, hospitalized patients with HFrEF, both with and without diabetes mellitus. Results from the study were presented as a Late Breaking Clinical Trial at the 2015 Scientific Sessions of the American Heart Association. The investigators found that the GLP-1 agonist liraglutide did not seem to improve posthospitalization clinical stability in patients with advanced HF.

Nevertheless, the metabolic pathways linking diabetes mellitus and HF will undoubtedly lead to additional, novel pharmacological approaches. Empagliflozin, an inhibitor of sodium-glucose cotransporter-2, was able to reduce the risk of the primary composite end point (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke), as well as some secondary end points, including all-cause death, cardiovascular death, and hospitalization for HF in diabetic patients at high cardiovascular risk.

Cardiac Devices
Unlike pharmacotherapy, device therapy for HF is invasive, expensive, and mostly irreversible, highlighting the need for accurate prediction of who will benefit before implantation. Devices in HF are typically considered after a background of optimal medical therapy has been implemented and include cardiac resynchronization therapy (CRT), implantable cardioverter-defibrillators (ICD), and VADs.

CRT and Beyond
CRT improves symptoms, survival, and quality of life in addition to salutary effects on cardiac function and structure. Patients who derive the most benefit include those with persistent NYHA functional class II–III symptoms despite optimal medical therapy, sinus rhythm with wide QRS complex, and severe left ventricular dysfunction. It is reported in the literature that up to one third of patients do not respond to CRT therapy. Debate continues on how to identify nonresponders, with most data focusing on QRS duration and morphology, NYHA functional class, and LVEF as reflected in the guidelines. A recent prespecified subgroup analysis of the Echocardiography Guided Cardiac Resynchronization Therapy (EchoCRT) study reported no benefit of CRT and possible harm with QRS <130 ms. A novel measure of electric dyssynchrony, the sum absolute QRST integral, was tested retrospectively in the SmartDelay Determined AV Optimization: A Comparison to Other AV Delay Methods Used in Cardiac Resynchronization Therapy (SMART-AV) study. Importantly, the sum absolute QRST integral can be measured from a standard 12-lead ECG and is a simplified measurement of action potential heterogeneity in the heart. In theory, multipolarity
of electric activation correlates with electric dyssynchrony. In this study, the sum absolute QRST integral was independently associated with CRT response.54

Often, implantation of a CRT device is accompanied by implantation of a defibrillator. A recent meta-analysis suggests that recovery of LVEF after CRT is associated with significantly reduced appropriate ICD therapy, particularly in a subset of patients with improvement in LVEF to ≥45% and ICD implanted as primary prevention.55 This study raises the question of whether continued ICD therapy is warranted in this group of patients who are at relatively low risk of ventricular tachyarrhythmias.

When we are able to accurately predict response to CRT before implantation, those who are in the subset of likely nonresponders will be prime targets for an alternative therapy. Cardiac contractility modulation has been proposed to fill this niche. Cardiac contractility modulation signals are nonexcitatory electric signals delivered during the absolute refractory period that serve to enhance cardiac contraction. The mechanism of action may affect regulation of calcium cycling.56 A randomized controlled trial evaluating safety and efficacy of this therapy is underway (Evaluate Safety and Efficacy of the OPTIMIZER® System in Subjects With Moderate-to-Severe Heart Failure [FIX-HF-5C] study), and results are forthcoming. Interestingly, this study included patients with normal QRS duration and LVEF from 25% to 45% with NYHA class III–IV symptoms.57 There are many devices being actively investigated to modulate the autonomic nervous system in patients with HF; including stimulation of the vagus nerve, carotid body, spinal cord, and renal denervation.58,59 The concept of rebalancing the sympathetic and parasympathetic nervous systems in chronic HF is intriguing; results of the Increase of Vagal Tone in Heart Failure (INOVA-THE-HF) study60 are anticipated in the next few years (Table 2).

Ventricular Assist Devices
Mechanical circulatory support with VADs for end-stage HF was first shown to be a life-saving therapy in 2001.61 During the past several years, the first generation pulsatile flow VADs have been replaced for the most part with continuous flow devices that are smaller and more durable. The Heartmate II left VAD (Thoratec, Inc) and HeartWare VAD (HeartWare, Inc) are the most commonly implanted second generation VADs presently. A recently completed but not yet published trial called a Prospective, Randomized, Controlled, Un-blinded, Multi-Center Clinical Trial to Evaluate the HeartWare Ventricular Assist System (VAS) for Destination Therapy of Advanced Heart Failure (ENDURANCE) was presented at the 35th International Society for Heart and Lung Transplantation Annual Meeting in 2015, reporting noninferiority of HeartWare VAD to Heartmate II in destination therapy patients (Table 2). However, in a multi-institution pooled analysis, a trend was found for higher incidence of driveline infections in patients with Heartmate II, and a higher incidence of stroke was found in patients treated with the HeartWare VAD.52 We continue to struggle to decide when to implant a VAD in the less sick cohort of patients with ambulatory severe HF, especially those who are not yet on inotropes. The recently published Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients (ROADMAP) observational study suggested benefit in terms of survival and quality of life despite increase in adverse events in patients who received a VAD compared with those treated with medical therapy.62 It is important to note that this study was observational and that the patients who received a VAD were sicker than those who received medical therapy.

Despite advances in technology, continuous flow VADs have considerable complications, including arteriovenous malformations, leading to gastrointestinal bleeding, hemorrhagic strokes, hemolysis, pump thrombosis, aortic valve insufficiency, and valve fusion.63,64 There is debate on how much diminished flow pulsatility and lower arterial pressure contribute to these complications.65 For example, a recent study investigating the effect of nonpulsatile and pulsatile flow on cerebral perfusion found that the magnitude of oscillation in arterial pressure and cerebral blood flow was greater in patients with continuous flow VADs compared with normal patients or those with pulsatile flow VADs. However, autoregulation of cerebral flow was preserved in both device types.67 Another intriguing study using a transparent replica of the HeartMate II left VAD (Thoratec, Inc) at different flow rates showed that pulsatility imposed on the system (in theory by the native heart) may induce disturbance to an otherwise stable flow field with possibly prothrombotic effects.68 This study is particularly interesting as a newly designed VAD, the HeartMate III (Thoratec Corporation, Pleasanton, CA), which is in clinical trials currently, aims to intermittently introduce pulsatility to a centrifugal pump system (Table 2).

There was considerable excitement in the potential for recovering myocardial function with VAD support in conjunction with pharmacological therapy, including the β2-agonist clenbuterol.69 However, enthusiasm has been tempered during the past several years by evidence of recovery on a cellular and molecular level without sustainable recovery on a macroscopic or organ level.70,71 Hence, a paradigm shift is underway, from a goal of myocardial recovery to one of the remodeling sufficient to allow for sustainable exploitation of the device even if cardiomyopathy remains.72 Neurohormonal blockade remains a cornerstone of management in conjunction with mechanical support to unload a failing heart and promote positive remodeling.73 The use of mesenchymal precursor cells may be a promising adjunctive therapy in this regard as recent data from Ascheim et al74 support.

Predicting the Course of the HF Syndrome and Monitoring for Intervention

Monitoring Devices
Hospitalization for HF is demoralizing for patients and contributes to their poor quality of life; it is an enormous component of the rising cost that many countries sustain to care for HF.75 Likewise, the repeated episodes of acute HF decompensation are thought to be a major source of progressive myocardial dysfunction via repeated subendocardial injury.76 Thus, a reasonable target for many clinical trials has been to show that an intervention reduces HF hospitalizations. Moreover, implantable devices have been designed to help detect the onset of HF instability before the development of the fully manifest decompensated HF syndrome.77 The hypothesis has been that
such early detection systems might prevent HF admissions and reduce mortality.

For many years, ICDs and CRT with and without ICDs have incorporated software that includes HF diagnostic data, such as hemodynamics (pressure or fluid index derived from intrathoracic impedance), correlates of physical activity,75 or autonometrics to predict HF events.79,80 Some clinicians and trials have found the addition of this information to be helpful in the assessment of patients with HF, but HF clinical practice guidelines have not considered their value highly. Rather than relying on a single parameter, Program to Access and Review Trending Information and Evaluate Correlation to Symptoms in Patients With Heart Failure (PARTNERS HF) evaluated the utility of combining several diagnostic modalities into an algorithm: long atrial fibrillation duration, rapid ventricular rate during atrial fibrillation, a high fluid index using the thoracic impedance methodology, low patient activity (using implanted device methodology), abnormal autonemics (high night heart rate or low heart rate variability), or notable device therapy (low CRT pacing or ICD shocks), or if they only had a very high fluid index.81 In the 694 patients studied for almost 12 months, a monthly review of HF device diagnostic data identified patients at a 5-fold higher risk of HF hospitalization in the subsequent month. Subsequently, 1562 patients were evaluated on the day of hospital discharge using a similar diagnostic algorithm. The investigators found that the device-derived data accurately predicted those patients at the highest risk of 30-day readmission.82 The algorithm has now been validated in a prospective fashion.83 Streamlining the collection of data and applying it in real time to focus resources on the most vulnerable patients are the presumed next steps.

A wireless hemodynamic monitor implanted in the pulmonary artery continuously measures pulmonary pressures in patients with HF and can provide the data quickly and repeatedly over months to years. The CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients (CHAMPION) trial evaluated the role of this device in 550 randomized HF patients with NYHA class III and any LVEF.84 The investigators were able to demonstrate a significant and clinically meaningful reduction in hospitalization for patients who were managed with the implantable hemodynamic monitoring system; this was true even in patients aged <75 years and overall reduced HF and cardiovascular hospitalizations.85 Another meta-analyses of individual patient data sought to investigate the interactions between age, comorbidities, or type of HF (preserved or reduced LVEF) and HF. The following year, an individual patient meta-analysis of natriuretic peptide–guided HF therapy revealed that all-cause mortality was significantly reduced in patients aged <75 years and overall reduced HF and cardiovascular hospitalizations.86,87

Biomarkers and Risk Prediction Models

The more accurate and reproducible diagnosis of myocardial infarction, initially with the analysis of the isoenzyme of creatine kinase and later with various forms of troponin, taught clinicians the remarkable utility of using biomarkers to buttress a clinical evaluation. As a result, there was tremendous enthusiasm for the potential of HF biomarkers after the ground-breaking publication showing the applicability of BNP to improve the diagnostic accuracy of HF in the emergency department.88 Since that time, there has been an explosion of investigations into a myriad of biomarkers.89,90 Biomarkers can be grouped into the physiological domains that they reflect, for example, inflammation or fibrosis, renal function, myocardial wall stress, or infection. More recently, micro-RNAs have been proposed as an even more precise biomarker, in 1 example to predict the response to CRT.89 The ultimate test, however, of any biomarker is to show that clinical knowledge of the same, and an appropriate intervention based on that knowledge, will change clinical outcomes when compared with the gold standard.89

The biomarkers that are used most often in the clinical arena include the natriuretic peptides, BNP or NTpro-BNP, which reflect myocardial stress or stretch.90 A systematic analysis of the incremental value of BNP or NTpro-BNP in predictive models of acute HF concluded that the literature was limited to 7 studies evaluating only mortality outcomes; all had moderate risk of bias.91 Nevertheless, they acknowledged that there was consistency in the added value to the measurement of natriuretic peptide in patients with acute HF. A more recent meta-analysis had a stronger conclusion: introduction of natriuretic peptide measurement in the investigation of patients with suspected acute HF has the potential to allow rapid and accurate exclusion of the diagnosis.92 A similar analysis concluded that the addition of NTpro-BNP to predictive models in chronic HF likewise improved accuracy.93 Indeed, clinicians worldwide use BNP or NTproBNP as a valuable tool to aid in the diagnosis of HF and to identify patients at higher risk of HF complications. A definitive trial demonstrating that the use of natriuretic peptides to guide HF therapy is significantly better than standard management algorithms alone has been more elusive.

One important trial, the St Vincent’s Screening to Prevent Heart Failure Study (STOP-HF),94 proved that a BNP-based screening of patients at risk of HF, combined with subsequent collaborative care, reduced the combined rates of cardiac remodeling (either with respect to systolic or diastolic dysfunction) and HF. The following year, an individual patient meta-analysis of natriuretic peptide–guided HF therapy revealed that all-cause mortality was significantly reduced in patients aged <75 years and overall reduced HF and cardiovascular hospitalizations.95 Another meta-analyses of individual patient data sought to investigate the interactions between age, comorbidities, or type of HF (preserved or reduced LVEF) and treatment response in the randomized trials of (NT-pro) BNP–guided therapy in HF.96 These authors concluded that the benefits of therapy guided by (NT-pro) BNP were present in HFrEF only. However, most investigators agree that the ongoing Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure (GUIDE-IT) trial (Table 2) will help clarify this important question. GUIDE-IT is designed to determine the safety, efficacy, and cost-effectiveness of a strategy of adjusting HF therapy with the goal of achieving and maintaining a target NT-proBNP level of <1000 pg/mL, compared with usual care in high-risk patients with HFrEF.97

Other biomarkers are under active investigation in smaller pilot trials but have yet to be incorporated into clinical practice guidelines as necessary for optimal management of patients
with HF. Soluble ST2 is a marker that evokes several mechanistic aspects of HF, including myocardial strain, remodeling, and fibrosis; soluble ST2 belongs to the interleukin-1 receptor family. This marker has been shown to have strong prognostic value for both acute and chronic HF, especially when the combination of ST2 and the natriuretic peptides is used. Cystatin C is a cysteine protease inhibitor that is produced continuously at a constant rate, freely filtered in the kidney, and not secreted in renal tubules; cystatin C is an accurate measure of glomerular filtration rate. During the past decade, cystatin C has been used extensively as a research tool for understanding how kidney function affects health outcomes. Galectin-3 is a member of the β-galactoside–binding lectin family found in many cell types, including fibroblasts and macrophages. This marker also has potential prognostic information, additive to NT-proBNP. Disappointingly, in a recent analysis of the prognostic role of galectin-3 in a trial of patients with HFpEF, galectin-3 levels were found to be associated with age and severity of renal dysfunction, but after adjusting for age, sex, or cystatin-C, galectin-3 was not associated with biomarkers of neurohumoral activation, fibrosis, inflammation or myocardial necrosis, congestion or quality-of-life impairment, cardiac remodeling or dysfunction, or exercise intolerance.

When 1 biomarker adds to a diagnostic algorithm, the use of a multimarker strategy might be more impactful. For example, an intriguing study demonstrated that early increases in multiple biomarkers predicted subsequent cardiotoxicity in patients with breast cancer treated with doxorubicin, taxanes, and trastuzumab. Likewise, combining biomarkers that measure myocardial wall stress and infection allows, for example, an assessment of the breathless patient to exclude HF and consider a bronchitis—an approach that substantially alters treatment. The enthusiasm for this methodology must be tempered with careful outcome trials to justify the additional cost of serial biomarkers.

HF is associated with high mortality, but the risk of death in an individual patient is not easily predictable. Accordingly, many risk models have been developed to help clinicians guide patients toward more advanced therapy or to make end-of-life decisions. A complete list of the currently used risk models is beyond the scope of this review. Two models are increasingly being used in both the clinical setting and incorporated into clinical trials: the Seattle Heart Failure Model and the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) score. Using either score is predicated on the assumption that the variables used are easily obtained during a typical HF evaluation. The Seattle Heart Failure Model is frequently used in the United States as a method to assess risk or need for heart transplant or VAD surgery; critics have suggested that further validation of the score in this population might be needed. The MAGGIC score, developed in Europe, is currently used to raise awareness of the poor prognosis of patients with HF who appear well compensated. There have been many analyses comparing one risk score with another in a variety of HF patient populations. Inevitably, information from biomarkers and other diagnostic testing have been added to the risk scores to examine the resultant change in predictive capability. This has prompted a cautionary note suggesting that the marginal benefit of complex prognostic evaluations must be balanced against potential patient discomfort and cost escalation. Current HF guidelines suggest that risk profiling may be helpful to inform patient decision making and guide clinical management.

Exercise Training
It is well recognized that regular physical activity or exercise training contributes substantially to the prevention and treatment of cardiovascular disease. For many years, patients with chronic HF were urged to perform regular aerobic activity. Cardiac rehabilitation has been convincingly shown to be effective in improving functional capacity and quality of life and to reduce HF hospitalizations in both patients with HFrEF and HFpEF. Indeed, the US Centers for Medicare and Medicaid Services has approved coverage for cardiac rehabilitation for stable outpatients with HFrEF. Sadly, only a small fraction of eligible patients are referred to cardiac rehabilitation; efforts are underway to ensure that exercise training becomes more routine.

Both the European and the American clinical practice guidelines are in the process of being updated to reflect some of the trials summarized above. A reasonable, stepped approach to the patient with HFrEF is depicted in (personal communication). Figure 3.

**Problem of the Patient With HFpEF**
Most of the major advances in HF management during the past 20 years have been for the patient with HFrEF. Yet, ≈50% of patients hospitalized with HF have a preserved LVEF. This journal has recently published 2 excellent reviews on the mechanistic aspects of HFpEF; HFpEF seems to be a different syndrome from HFrEF. Paulus and Tschöpe have sought to translate the observation that patients with HFpEF have multiple comorbidities into a novel pathophysiologic explanation of the disease. They hypothesize that the comorbidities that typically include diabetes mellitus, hypertension, and obesity lead to a systemic proinflammatory state, which in turn leads to microvascular endothelial inflammation. The vascular inflammation reduces nitric oxide bioavailability, cyclic GMP content, and protein kinase G activity in adjacent cardiomyocytes. The resulting low protein kinase G activity favors hypertrophy development and increases myocardial resting tension because of hypophosphorylation of titin. The attractive nature of this hypothesis is that many potential new targets for treatment can be imagined. This is critically needed, as the current landscape of HFpEF trials has been littered with neutral or negative outcomes, as shown in Table 3.

One trial included in Table 3, Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT), explored the use of an aldosterone antagonist in patients with HFpEF, enrolling 3445 participants from 6 countries. The use of spironolactone did not achieve a significant reduction in the primary outcome, a composite of cardiovascular death, aborted cardiac arrest, or HF hospitalization compared with placebo. Interestingly, in a post hoc analysis, a marked and statistically significant difference was noted in prognosis, event rate, and response to the aldosterone antagonist between the
1678 patients randomized from Russia and Georgia compared with the 1767 enrolled from the United States, Canada, Brazil, and Argentina (called the Americas by the authors). This became critically important because Russia and Georgia contributed 49% of the total enrollment. The authors reflected in their discussion a point that is often lamented: making the assessment that the dyspnea and fatigue of a patient with a preserved ejection fraction are attributed to HF rather than to the commonly associated comorbidities is notoriously difficult. These results underscore one of the problems in finding effective treatments for the patient with HFpEF—do they really have HF?

In particular, the poor exercise tolerance of patients with HFpEF has been the focus of recent investigation, exploring the benefits of exercise training or using exercise duration as an end point with novel therapies. Most recently, another trial of the National Heart, Lung, and Blood Institute Heart Failure Network, the Nitrate’s Effect on Activity Tolerance in Heart Failure with Preserved Ejection Fraction (NEAT-HFpEF) trial asked patients with HFpEF to wear an activity accelerometer belt to accurately measure daily exercise. Unfortunately, patients who received the oral nitrate were less active and did not enjoy better quality of life or submaximal exercise capacity compared with patients who received placebo. Although the trial was negative, it certainly provides a clinical rationale to avoid the use of nitrates in patients with HFpEF.

The vast majority of patients with HFpEF are not candidates for advanced therapies, such as VAD or heart transplant, usually because of their age. Moreover, left VADs are not well suited for patients with nondilated left ventricles. However, some younger patients with HFpEF are transplanted, typically those with either restrictive or hypertrophic cardiomyopathies. Currently, there is much overlap in our approach to both types of patients. Many clinicians use therapies proven to be effective in patients with HFrEF for their patients with HFpEF; the data supporting this approach are not robust in most cases.

Figure 3. Approach to the patient with heart failure with reduced ejection fraction. ACE indicates angiotensin-converting enzyme; ICD, implantable cardioverter defibrillator; and NYHA, New York Heart Association.
Table 3. Summary of Randomized Trials in Patients With Symptomatic HfPEF

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year Published</th>
<th>Drug (s) Tested</th>
<th>No. of Patients</th>
<th>% Female, Drug/Placebo</th>
<th>LVEF (%), Inclusion Criterion</th>
<th>Actual Mean, LVEF (%), Drug/Placebo</th>
<th>Months Follow-Up</th>
<th>End Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHARM</td>
<td>2003</td>
<td>Candesartan vs placebo</td>
<td>3023</td>
<td>≥40 31.2/32.0</td>
<td>38.8/38.8</td>
<td>37.7 (median)</td>
<td>No difference in mortality; MI treatment group had fewer hospitalizations for HF</td>
<td></td>
</tr>
<tr>
<td>PEP-CHF</td>
<td>2006</td>
<td>Perindopril vs placebo</td>
<td>580</td>
<td>&gt;40 54/57</td>
<td>65/64</td>
<td>25 (median)</td>
<td>Insufficient power to assess the end point: all-cause mortality and HF hospitalization</td>
<td></td>
</tr>
<tr>
<td>DIG-PEF</td>
<td>2006</td>
<td>Digoxin vs placebo</td>
<td>988</td>
<td>&gt;45 42.1/40.3</td>
<td>55.4/55.5</td>
<td>37 (median)</td>
<td>No difference in mortality or all-cause hospitalization</td>
<td></td>
</tr>
<tr>
<td>I-PRESERVE</td>
<td>2008</td>
<td>Ibesartan vs placebo</td>
<td>4128</td>
<td>≥45 59/61</td>
<td>59/60</td>
<td>49.5 (median)</td>
<td>No difference in mortality or any CV hospitalization</td>
<td></td>
</tr>
<tr>
<td>SENIORS</td>
<td>2009</td>
<td>Nebivolol vs placebo</td>
<td>752</td>
<td>&gt;35 50.8</td>
<td>49.3/49.1</td>
<td>21 (median)</td>
<td>No difference in mortality or any CV hospitalization</td>
<td></td>
</tr>
<tr>
<td>RAAM-PEF</td>
<td>2011</td>
<td>Eplerenone vs placebo</td>
<td>44</td>
<td>≥50 4.8/8.7</td>
<td>62.1/62.5</td>
<td>6</td>
<td>Improvement in LV diastolic function and serum markers of collagen turnover; no difference in 6-min walk distance</td>
<td></td>
</tr>
<tr>
<td>ELANDD</td>
<td>2012</td>
<td>Nebivolol vs placebo</td>
<td>116</td>
<td>≥45 65/64</td>
<td>61.9/63.2</td>
<td>6</td>
<td>No difference in QOL, NYHA class, peak oxygen uptake or 6-min walk distance</td>
<td></td>
</tr>
<tr>
<td>PARAMOUNT</td>
<td>2012</td>
<td>LCZ696 vs valsartan</td>
<td>301</td>
<td>≥45 57.5/65/65/65</td>
<td>58/58</td>
<td>9</td>
<td>LCZ696 reduced NT-proBNP to a greater degree than valsartan</td>
<td></td>
</tr>
<tr>
<td>Aldo-DHF</td>
<td>2013</td>
<td>Spiranolactone vs placebo</td>
<td>422</td>
<td>≥50 52/53</td>
<td>67/68</td>
<td>12</td>
<td>Improvement in LV diastolic function spiranolactone group; no difference in QOL</td>
<td></td>
</tr>
<tr>
<td>J-DHF</td>
<td>2013</td>
<td>Carvedilol vs placebo</td>
<td>245</td>
<td>≥40 42.5/41.6</td>
<td>62/63</td>
<td>38 (median)</td>
<td>Group on &gt;7.5 mg daily had significant improvement in composite end point of CV death or HF hospitalization; group on ≤7.5 mg daily had no difference</td>
<td></td>
</tr>
<tr>
<td>RELAX</td>
<td>2013</td>
<td>Sildenafil vs placebo</td>
<td>216</td>
<td>≥50 49/55</td>
<td>60/60</td>
<td>6</td>
<td>No difference in peak oxygen consumption or clinical status</td>
<td></td>
</tr>
<tr>
<td>RELAX-AHF</td>
<td>2014</td>
<td>Sereloxin vs placebo</td>
<td>281 HfPEF group</td>
<td>≥50 58.4</td>
<td>58.7</td>
<td>180 (d)</td>
<td>Treatment of acute heart failure with sereloxin was associated with relief of dyspnea but no effect on 60-d readmissions or 180-d mortality</td>
<td></td>
</tr>
<tr>
<td>TOPCAT</td>
<td>2014</td>
<td>Spiranolactone vs placebo</td>
<td>1722</td>
<td>≥45 51.6/51.5</td>
<td>56/56</td>
<td>39.6 (mean)</td>
<td>No difference in the composite end point of CV death or HF hospitalization; spiranolactone group had a lower incidence of HF hospitalization</td>
<td></td>
</tr>
</tbody>
</table>

Aldo-DHF indicates Aldosterone Receptor Blockade in Diastolic Heart Failure; CHARM, Candesartan in Patients With Chronic Heart Failure and Preserved Left Ventricular Ejection Fraction; CV, cardiovascular; DIG-PEF, Digoxin on Morbidity and Mortality in Diastolic Heart Failure: the Ancillary Digitalis Investigation Group Trial; ELANDD, Effect of Long-Term Administration of Nebivolol on Clinical Symptoms, Exercise Capacity and Left Ventricular Function in Patients With Diastolic Dysfunction; HF, heart failure; HfPEF, HF with preserved ejection fraction; I-PRESERVE, Ibesartan in Heart Failure With Preserved Systolic Function; J-DHF, Japanese Diastolic Heart Failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PARAMOUNT, Prospective Comparison of ARNI With ARB on Management of Heart Failure With Preserved Ejection Fraction; PEP-CHF, Perindopril in Elderly People With Chronic Heart Failure; QOL, quality of life; RAAM-PEF, Randomized Aldosterone Antagonism in Heart Failure With Preserved Ejection Fraction; RELAX, Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure With Preserved Ejection Fraction; RELAX-AHF, Sereloxin, Recombinant Human Relaxin-2, for Treatment of Acute Heart Failure; SENIORS, Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure; and TOPCAT, Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist.

annotation, functional status) classification, was proposed in 2014.126 Although cumbersome at first glance, this scheme incorporates not only the standard morphofunctional attributes of cardiomyopathy but also the increasingly important pathologic (genetic, environmental, etc) and spectrum of functional status, including preclinical disease (genotype positive and phenotype negative). A classification scheme that provides a common language among clinicians and scientists promotes collaboration and discovery, as illustrated in a recent study by Hazebroek et al.127

An important example highlighting the need for deep phenotyping is the rapidly unfolding pathophysiology of arrhythmogenic right ventricular cardiomyopathy (ARVC). The presence of cardiotoxic viruses was documented in patients with ARVC by Bowles et al.126 in 2002; however, the pathophysiologic role was unknown. During the past decade, genetic testing for ARVC has demonstrated a pathogenic mutation in desmosomal or nondesmosomal genes in >50% of patients.129

Groundbreaking work by Kim et al.130 in 2013 using patient-specific, induced pluripotent stem cells demonstrated the requirement of both pathological genotype and metabolic derangement to recapitulate the ARVC disease state in an in vitro model. A zebrafish model of ARVC with cardiac myocyte–specific expression of the human 2057del2 mutation in the gene-encoding plakoglobin was developed by Asimaki et al.131 allowing for a platform of high throughput screening. This study identified a small molecule that rescues the phenotype, moving ever closer...
to a therapeutic target in humans that addresses the molecular basis of disease. An intriguing recent finding by the Lopez-Ayala et al. circles back to the role of myocarditis in ARVC, notably reporting an association between acute episodes of myocarditis and the progression of underlying disease. Furthermore, it may be the case that certain mutations increase susceptibility to an environmental insult, such as viral myocarditis. The theme of abnormal genotypic backdrop and subsequent environmental insult triggering presentation or progression of phenotype is likely to be common among many forms of cardiomyopathy on further investigation. Certainly, there are emerging associations reclassifying peripartum cardiomyopathy as part of familial dilated cardiomyopathy. Although not yet properly investigated, it is conceivable that genetic mutations that predispose to dilated cardiomyopathy may also increase the risk of developing anthracycline-associated cardiomyopathy. Increasing availability of high throughput, affordable next generation sequencing platforms will promote investigation of these theories with subsequent testing of newly discovered genes/mutations in patient-specific models. The therapeutic implications of being able to deeply phenotype and target research and subsequent pharmacological therapy to-at-risk individuals or those in early stages of disease will be an exciting frontier of investigation and treatment in the coming years.

Disclosures

None.

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Anjali Tiku Owens, Susan C. Brozena and Mariell Jessup

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