Curr Cardiol Rep (2017) 19: 103
DOI 10.1007/s11886-017-0900-8

HEART FAILURE (HJ EISEN, SECTION EDITOR)

The Initial Evaluation and Management of a Patient with Heart Failure

Jamael Hoosain[1] · **Jabar Whittier**[1] · **Farhan Hasni**[1] · **Shelley Hankins**[1]

Published online: 6 September 2017

Abstract
Purpose of Review The goal of this review is to summarize and discuss a thorough and effective manner in the evaluation of the patient with heart failure.
Recent Findings Heart failure is a prevalent disease worldwide and while the diagnosis of heart failure has remained relatively unchanged via a careful history and physical examination, identification of the etiology of the heart failure and treatment has made significant advances. Mechanical circulatory support (MCS), neprilysin inhibitors, and chronic resynchronization therapy (CRT) are just some of the relatively recent therapies afforded to assist heart failure patients.
Summary Heart failure is a complicated, multifactorial diagnosis that requires a careful history and physical for diagnosis with the support of laboratory tests. While the prognosis for heart failure patients remains poor in comparison to other cardiovascular disease and even certain cancers, new advancements in therapy have shown survival and quality of life improvement.

Keywords Heart failure · Cardiomyopathy · Hypertension

This article is part of the Topical Collection on *Heart Failure*

✉ Shelley Hankins
shankins@drexelmed.edu

Jamael Hoosain
Jah446@drexel.edu

Jabar Whittier
Jabar.Whittier@drexelmed.edu

Farhan Hasni
Sfh28@drexel.edu

[1] Drexel University College of Medicine, 245 N 15th Street, Philadelphia, PA 19102, USA

Abbreviations

HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
LVEF	Left ventricular ejection fraction
NYHA	New York Heart Association
BNP	B-type natriuretic peptide
NT-proBNP	N-terminal pro-B-type natriuretic peptide
ADHF	Acute decompensated heart failure
ICD	Implantable cardioverter-defibrillator
CRT	Cardiac resynchronization therapy
LBBB	Left bundle branch block
ACE	Angiotensin-converting enzyme
ARB	Angiotensin-receptor blockers
RAAS	Renin-angiotensin-aldosterone system
MRA	Mineralocorticoid receptor antagonist
MCS	Mechanical circulatory support
LVAD	Left ventricular assist device
BIVAD	Biventricular assist device
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support

Introduction

Heart failure (HF) is a complicated clinical diagnosis that results from impaired ventricular relaxation or contraction [1]. Heart failure affects 5.8 million people in the USA and 23 million people worldwide [2]. The evaluation of the patient with heart failure begins with a careful history and physical examination along with support from diagnostic tests.

The history should comprise a comprehensive review of the type of symptoms the patient has been experiencing, the duration, and the severity of symptoms. Common complaints of patients with HF include fluid retention, decreased exercise

tolerance, fatigue, and dyspnea or shortness of breath [3]. In addition, key features should be discussed such as shortness of breath when lying flat and/or waking up in the middle of the night short of breath, which are known as orthopnea and paroxysmal nocturnal dyspnea, respectively [2, 3].

Causes of heart failure vary in etiologies and manifestations. Heart failure etiologies can be ischemic, non-ischemic from viruses, metabolic disorders, or large vessel disease, pericardial disease, or valvular disease [4, 5]. Manifestations of these diseases can cause impaired ventricular relaxation, impaired ventricular contraction, or a combination of both [6]. The preferred terms to address heart failure patients with these conditions are heart failure with reduced ejection fraction (HFrEF) for subjects with impaired ventricular contraction and heart failure with preserved ejection fraction (HFpEF) for subjects with impaired ventricular relaxation [7]. Ejection fraction is a key component in the terminology because of the clinical trials utilizing ejection fraction for prognosis [8].

HFrEF is defined as a left ventricular ejection fraction (LVEF) $\leq 35\%$ [5, 7]; whereas, HFpEF can be defined as LVEF $\geq 55\%$. Patients with an LVEF between these two numbers fall in a transitional zone.

Objective criteria in the assessment of heart failure include the ACC/AHA stages of heart failure and the New York Heart Association (NYHA) functional classification [9]. The ACC/AHA stages focus on prevention and progression of the disease state while the NYHA classes characterize symptoms. Furthermore, the ACC/AHA stages are permanently progressive and as patients move forward in stages they cannot regress; however, patients in the NYHA classes can matriculate forward and back through the classes based on their symptoms. The ACC/AHA stage advancement is from stage A in patients with risk factors but without structural heart disease, to stage B with structural heart disease but absent of symptoms, to stage C with structural heart disease and symptoms of HF, and finally to stage D with structural heart disease that is refractory to medical therapy. NYHA classes range from class I defined as no limitation in physical activity, to class IV where symptoms of HF are present even at rest; these functional classes are predictors of mortality [10].

Causes of Heart Failure

Heart Failure causes can be divided into several different categories but first it behooves the clinician to evaluate risk factors for heart failure. Hypertension, diabetes, and dyslipidemia are all modifiable risk factors that can reduce or prevent heart failure progression [11]. Hypertension is the greatest risk to heart failure development, and treatment can significantly reduce the chances of HF [10–12].

Categorization of cardiomyopathies has been a subject of debate as knowledge in the field grows [4, 5, 7]. The ACCF/AHA Heart Failure Guideline differentiates cardiomyopathies into dilated, familial, metabolic, toxic, tachycardia-induced, inflammation, peri-partum, and others [6]; whereas traditionally, patients are defined by dilated, restrictive, or hypertrophic cardiomyopathies. Defining the etiology of heart failure in a patient with his/her appropriate cardiomyopathy is paramount in guiding treatment strategies.

In a study of 156,013 heart failure patients, the majority of dilated cardiomyopathies were idiopathic (30.7%) [13]. Dilated cardiomyopathy can furthermore be subdivided into viral, post-partum, chemotherapy-induced, familial, and substance abuse related. Common viral cardiomyopathies include Coxsackie virus, Echovirus, Epstein-Barr virus, and many others that often go unrecognized until signs and symptoms of heart failure develop [14]. Post-partum cardiomyopathy-causing LV dysfunction is of unknown origin. Prognosis is improved in patients with recovered LV function compared to those without recovery or worsening LV function [15, 16]. Anti-neoplastic chemotherapy drugs cause a dilated cardiomyopathy due to their cardiotoxic properties. The predominant culprit out of these medications is the anthracycline class but also includes cyclophosphamide, trastuzumab, 5-FU, and the interferons [17].

Familial cardiomyopathy is defined as patients with two family members with idiopathic dilated cardiomyopathy [18]. Alcohol is the number one drug for substance abuse-related cardiomyopathy [19]. Identification of patients at risk for substance abuse is key to counseling for cessation that will improve symptoms and may reverse the disease process.

Initial Evaluation of the HF Patient

The diagnosis of heart failure can be established with a combination of findings on a comprehensive history and a focused physical exam with the utilization of additional laboratory findings. There have been several clinical scoring systems which have been developed through population-based studies as a means of screening, such as the Framingham criteria and the National Health and Nutrition Survey (NHANES) criteria. The Framingham criteria establishes a diagnosis with major and minor criteria of history and exam findings which include paroxysmal nocturnal dyspnea, orthopnea, jugular vein distention, an S3 gallop, rales, dyspnea on exertion, tachycardia, weight gain, and ankle edema; while the NHANES criteria utilizes self-reporting of severity of symptoms with physical exam findings as well as chest radiographic findings. Though there is a vast array of symptoms that help establish the diagnosis of heart failure, there are no specific symptoms to differentiating between HFpEF and HFrEF [4].

Outside of symptoms, a thorough history includes past medical conditions, family history, social history (e.g., alcohol and drug abuse), and exposure to medications with known cardiotoxicity such as chemotherapeutic agents, diabetic drugs

(e.g., thiazolidinediones), ergot-based antimigraine drugs, nonsteroidal anti-inflammatory drugs (NSAIDS), certain antipsychotic agents (ex. clozapine), as well as herbal remedies [4].

Many symptoms overlap with other medical conditions and thus the physical exam is a paramount component of establishing a diagnosis of heart failure as well as assessing the severity of an exacerbation. Physical exam findings of elevated jugular venous pressure, rales, wheezing, dullness, and diminished breath sounds at one or both lung bases, S3 and/or S4, tricuspid or mitral regurgitant murmurs, hepatomegaly, anasarca, and pedal edema with/without chronic venous stasis changes are suggestive of elevated cardiac chamber pressures and a volume-overloaded state. Aortic stenosis and regurgitation murmurs may represent a potential cause of heart failure and may drastically change management. Findings of resting tachycardia, hypotension, narrow pulse pressure or thread pulse, tachypnea, depressed mental status, decreased urine output, and cool and/or mottled extremities are not only suggestive of volume overload but may also represent a low cardiac output state [4]. Periodic or cyclic respiration or Cheyne-Stokes respiration is common in low cardiac output state and indicative of a worse prognosis [20]. As with symptoms, there are no specific physical findings that differentiate between HFpEF vs HFrEF [21].

Based on findings from the ESCAPE trial, the presence of orthopnea and findings of jugular vein distention are very sensitive in evaluating for elevated left-sided filling pressures. For example, orthopnea, as defined as requiring greater or equal to two pillows, was found to have a sensitivity of 86%. Jugular vein distention alone has a good sensitivity and specificity (70 and 79%, respectively) for elevated left-sided filling pressures, and with the addition of exerting pressure on the right upper quadrant (hepatojugular reflux), the sensitivity and specificity increases. Limitations to these exam findings include pronounced body habitus and conditions that cause jugular vein distention without increased left-sided chamber pressures, such as pulmonary arterial hypertension and isolated severe tricuspid regurgitation. Of note, findings of rales, hepatomegaly, and ascites are all highly specific [22]. With the rapid assessment of systemic congestion in conjunction with the recognition of reduced cardiac output states, patients can then be appropriately triaged into the following categories of severities of exacerbations: "Warm/Dry" (normal perfusion and uncongested), "Warm/Wet" (normal perfusion and congested), "Cold/Dry" (hypoperfused and uncongested), and "Cold/Wet" (hypoperfused and congested/cardiogenic shock) [23].

Laboratory Testing

The initial laboratory evaluation of patients in whom heart failure is suspected should comprise of a complete blood count to assess for anemia, a complete metabolic panel to assess electrolytes (including magnesium and calcium), serum glucose and renal and hepatic function, and a B-type natriuretic peptide. When clinically relevant, screening or diagnostic testing for HIV, hemochromatosis, tuberculosis, rheumatologic disease, amyloidosis, or pheochromocytoma may help establish systemic diseases with cardiac manifestations. Additional testing on the initial evaluation includes a thyroid-stimulating hormone and a fasting lipid profile. Serial monitoring of the serum electrolytes and renal function when treatment has been initiated is appropriate as well [7].

Biomarkers

Over the past decade, many serum biomarkers have been developed which provide supplemental means of evaluating patients with HF with respect to establishing a diagnosis, elucidating the pathogenesis of HF, providing prognostic data, risk stratification, and potential therapeutic targets. Examples of which include c-reactive protein, interleukins 1, 6, and 8, oxidized low-density lipoproteins, myeloperoxidase, matrix metalloproteinases, neurohormones of the renin-angiotensin-aldosterone system, troponin I and T, natriuretic peptides, chromogranin, and many more [24]. In the near future, with more multi-center studies with validation, well-defined outcome measures, and prognostic accuracy, utilizing combinations of existing and emerging biomarkers may become the new standard of care [25, 26••].

The development of serum biomarker assays for B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) have not only dramatically improved the efficiency of establishing the diagnosis and the initial management of HF, both in the chronic ambulatory and ADHF settings, but also provide valuable prognostic data that may be utilized for screening purposes [25, 26••]. Both biomarkers are released from the cardiomyocytes in response to stretch and increase progressively with worsening NYHA functional class and in acute decompensated HF (ADHF). Clinical data supporting the use of these biomarkers comes from multiple studies, including the Breathing Not Properly trial for BNP which found that a serum concentration of 100 pg/mL was highly accurate for the diagnosis of ADHF while in the ProBNP Investigation of dyspnea in the Emergency Department (PRIDE) studies, a cut-off of 900 pg/mL of serum NT-proBNP was comparable to in performance to a BNP of 100 pg/mL. In the International Collaborative of NT-proBNP study (ICON), an NT-proBNP below 300 pg/mL was useful in excluding the diagnosis of ADHF in the appropriate clinical context [4, 27].

Based on current guideline recommendations, checking serum concentrations of BNP and NT-proBNP on hospital admission is beneficial in the setting of acute dyspnea when

ADHF is suspected, as well as pre-discharge and in the chronic ambulatory setting to use as a benchmark for establishing prognosis [26••]. At this time, despite numerous studies, there is no consistent evidence for serum concentration guided therapy or serial measurements of BNP or NT-proBNP with respect to improvement in mortality and cardiovascular outcomes [26••, 28•, 29].

There are numerous covariates and other medical conditions, both cardiac and non-cardiac that cause an elevated BNP and NT-proBNP serum concentrations. Examples of which include valvular heart disease, acute coronary syndrome, atrial arrhythmias, left ventricular hypertrophy, right ventricular dysfunction, myocarditis, pericardial processes, toxic metabolic myocardial insults (e.g., chemotherapeutic agents), pulmonary hypertension, advanced age, anemia, renal failure, hypoxia, sepsis, and critical illness [26••, 30]. Obesity, on the other hand, is strongly linked with a lower-than-expected BNP or NT-proBNP, modestly reducing specificity [4, 29].

Non-invasive and Invasive Evaluation of Heart Failure Patients

In addition to history, physical exam, and laboratory testing, both non-invasive and invasive evaluations of the cardiac structure and function are needed to confirm the diagnosis and guide the initiation of therapies. On the initial evaluation, a 12-lead electrocardiogram and chest X-ray are reasonable to obtain. The 12-lead electrocardiogram may provide insight into the etiology of HF or possible explanations for an acute decompensation. The presence of Q-waves in the appropriate setting is suggestive of ischemic heart disease as an etiology of HF, while dynamic ST changes may indicate acute coronary ischemia, which could provoke acute decompensation. Sinus tachycardia and atrial arrhythmias may be seen in episodes of ADHF, especially in the setting of atrial arrhythmias with rapid ventricular responses. Sinus tachycardia in the ambulatory population is seen in advanced HF. The presence of increased QRS voltages may suggest structural disease such as left ventricular hypertrophy, hypertrophic cardiomyopathy, or pulmonary hypertension if there is evidence of right ventricular hypertrophy. Low QRS voltages may represent infiltrative disease or a pericardial effusion. The prolongation of the PR interval may be due to infiltrative disease or intrinsic conduction disease. Prolongation of the QT interval can occur frequently in patients with HF, which may represent myocardial disease, electrolyte abnormalities, or may be prolonged due to the use of anti-arrhythmic drugs. The QRS duration not only provides information for potential causes of the HF but may also affect the therapeutic approach with respect to device-based therapies [4].

Plain chest complement provided supplemental data with regards to assessing for signs of ADHF, which range from subtle findings of increased interstitial markings, peribronchial cuffing, and increased prominence of upper lobe vasculature to the less subtle pulmonary edema and pleural effusions. Other utilities include assessment for alternative cardiac, pulmonary, or other diseases. In cases of advanced heart failure, patients may have normal chest radiography or an electrocardiogram with non-specific or no abnormalities despite marked symptoms, thus the negative predictive values of both tests are too low to be used to exclude HF [31].

Assessment of left ventricular function plays a pivotal role in the management strategies with respect to classification of HFpEF or HFrEF. When there are significant changes in clinical status, repeat assessment of the LVEF and measurements of the severity of structural remodeling is recommended. Significant changes range from deterioration or worsening of symptoms, response to therapy, especially therapies that significantly affect cardiac function, and to evaluate for potential recovery of function. Without changes in clinical status or treatment interventions, serial assessments of LVEF provide no benefit. Repeat assessments of LVEF also determine candidacy for patients that will benefit from device-based therapy [7].

Two-dimensional echocardiogram with Doppler is one of the most versatile and readily available forms of non-invasive assessment of cardiac function. Two-dimensional echocardiography provides visualization of the cardiac chamber size, thickness, function, wall motion, diastolic function, intracardiac pressures, and valve function. Other non-invasive methods of evaluating LVEF can be utilized with echocardiography to provide an adequate assessment. Examples include radionuclide ventriculography, positron emission tomography, computed tomography, or magnetic resonance imaging. Magnetic resonance imaging provides high-quality imaging of the heart and additional benefits in assessing the myocardium for infiltrative processes, scar burden, and myocardial viability [4, 7].

Non-invasive imaging evaluation for ischemia and viability is reasonable for the initial evaluation for a potential explanation for a new diagnosis of HF, in particular those with the known coronary artery disease without angina symptoms. If there is reversible ischemia on non-invasive imaging, history of angina pectoris or cardiac arrest or if the cause of the ADHF was due to acute coronary syndrome or symptomatic ventricular arrhythmia, coronary angiography is reasonable for patients who are suitable for revascularization. As an adjunct, assessment of viability is also reasonable in patients with CAD and HF when planning revascularization [4, 32••].

As mentioned earlier, assessing the exercise tolerance is paramount to management of a patient with HF; however, quantification of such is subjective and can be inconsistent even with the use of the NYHA criteria and a 6-min walk test.

More precise measures of functional capacity can be provided by cardiopulmonary exercise testing and are needed for assessing candidacy for advanced therapies such as mechanical circulatory support or heart transplant.

There have been so many advances in non-invasive imaging techniques and use of biomarkers, the routine use of right heart catheterization for the measurements of intracardiac pressures, and hemodynamics for the initial evaluation of a patient with HF has fallen out of favor with few exceptions. Right heart catheterization still serves a role on the initial evaluation with patients in acute respiratory distress or with clinical evidence of impaired perfusion in whom intracardiac filling pressure is difficult to determine on clinical assessment. During a right heart catheterization, a pulmonary capillary wedge pressure is obtained which estimates left ventricular end-diastolic pressure, if there is no obstruction of flow between the left atrium and ventricle. Invasive hemodynamic monitoring with a pulmonary artery catheter may benefit patients presenting as ADHF with persistent symptoms despite standard therapies and whose volume status, perfusion, or pulmonary vascular resistance is uncertain, persistent hypotension with associated symptoms despite standard therapy, whose renal function is worsening with therapy, or those who require parenteral vasoactive agents. Despite the amount of information obtained from invasive hemodynamic measurements, there was no clear morbidity or mortality benefit in pulmonary artery pressure-guided management of ADHF in comparison to clinical assessment in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial [33]. There is no benefit of invasive hemodynamic monitoring in patients with normotensive ADHF who are responding to diuretics and vasodilators [34].

Risk Stratification

Once the diagnosis of HF has been established, there are many different multivariable risk scores that are helpful in stratifying risk of mortality in both the hospitalized and outpatient settings. Some examples include the EFFECT risk score, ESCAPE Risk model, and ADHERE classification in hospitalized patients and the Seattle Heart Failure model, Heart Failure Survival score for patients, and the I-PRESERVE Score (which is specific to HFpEF) for ambulatory patients [7].

Goal-directed Medical Therapy for Treatment

The next appropriate step in the management of HF patients is naturally the treatment of the condition. The primary goals are to improve symptoms, survival, and the quality of life. Additional goals include prevention of disease progression and possible recovery of LVEF. The therapies can be sorted into pharmacologic, device-based, and surgical therapies. The vast majority of recommendations for therapies are in HFrEF patients. Initiation of therapies is dependent on a combination of factors, but is primarily dependent on the AHA staging and baseline NYHA symptoms for chronic HF patients.

Stage A HF

In stage A HF patients, the main focus is management of modifiable risk factors, controlling comorbidities, and avoidance of exposures that are known to contribute to the risk of developing HF. Life style modifications include diet and exercise, smoke cessation, and treating lipid disorders, diabetes, and hypertension to meet contemporary guidelines which is beneficial in this group [7]. At this time, based on a large randomized control trial, hypertension should be controlled to less than 130/80 mmHg.

Stage B HF

For stage B HF patients, the main goal in this group is to prevent disease progression and improve survival. This is achieved by targeting neurohormonal-mediated cardiac remodeling and controlling the risk factors mentioned in stage A HF patients. In all HFrEF patients and in patients with history of MI or recent ACS with left ventricular dysfunction, angiotensin-converting enzyme (ACE) inhibitors are highly recommended to prevent progression of left ventricular dysfunction and reduce mortality [35–37]. If intolerant to ACE inhibitors, switching to angiotensin-receptor blockers (ARB) is appropriate unless there is a contraindication [38, 39]. The combination of both an ACE inhibitor and an ARB should be avoided at all cost as this has been proven hazardous.

In all HFrEF patients, especially with history of ischemic heart disease, patients receive a proven mortality benefit from evidence-based beta blockers [40–42]. Carvedilol, metoprolol succinate, and bisoprolol currently are the only three beta blockers with proven mortality benefit in this patient population [40, 43–46]. Ischemic heart disease patients benefit from the addition of statins to the regimen as well [47, 48]. In stage B ischemic heart disease patients, the placement of an implantable cardioverter-defibrillator (ICD) is reasonable to prevent sudden cardiac death in patients who are at least 40 days post-MI with an LVEF less than 30% and are on the appropriate medical therapy with a life expectancy greater than 1 year [7].

Stage C HF

Based on the latest iterations of the guidelines and emerging data, at this point the therapeutic options must be tailor-based

on if the patient has HFrEF or HFpEF. The vast majority of literature has been based on HFrEF, providing a plethora of therapeutic options with supportive data; however, there have been some significant data supporting treatment strategies in HFpEF patients.

Once stage B HFrEF patients develop symptoms (NYHA II-IV), they are reclassified to stage C HFrEF. This group of patients has a wide variety of therapeutic options. In addition to the treatments mentioned in stage A and B HFrEF patients, the clinician must alleviate the symptoms, which is achieved by reducing the effective workload by decreasing afterload and alleviating fluid retention.

Diuretics, in particular loop diuretics are the main therapy to alleviate patients of excessive volume and congestions via salt and water excretion. When managing patients with ADHF in the inpatient setting, the prompt use of intravenous loop diuretics reduces morbidity. Often times, these patients are already on a chronic oral dose of diuretics, in which the initial inpatient intravenous dose should be equal or exceed their chronic dose. Further dosages, either as intermittent bolus or continuous intravenous drip, should be adjusted accordingly with the goal of improving symptoms, reducing congestion, and improving perfusion while avoiding hypotension and over diuresis [49]. This is achieved through serial monitoring of the changes in the signs and symptoms of congestion, vital signs, fluid intake and urine output, daily weights, urea nitrogen, creatinine, and serum electrolytes [32••].

If there is a suboptimal response, the dose could be increased or an addition of a thiazide diuretic may be beneficial. Low-dose dopamine may be a reasonable addition to improve diuresis, which may preserve renal function/blood flow [49–54]. If there is still refractory congestion despite medical therapy or renal failure has occurred, ultrafiltration or renal replacement therapy for fluid removal may be appropriate [55]. In a select population of patients, a vasopressin antagonist may be considered in short-term use to increase free-water excretion while improving serum-sodium concentrations in volume-overloaded HF patients with severe hyponatremia, who are at risk or are experiencing cognitive symptoms despite maximum medical therapies [32••, 56, 57].

Recently, a new modality to promote renin-angiotensin-aldosterone system blockade has emerged. The combination of sacubitril (neprilysin inhibitor) and valsartan (ARB) is a new compound that is referred to as an ARNI or angiotensin receptor neprilysin inhibitor. The ARB acts on the RAAS while the neprilysin inhibitor acts on the neutral endopeptidase, preventing the breakdown of natriuretic peptides (A-type natriuretic peptide and BNP), bradykinin, and other peptides. The increase in natriuretic peptides augments the generation of cGMP, which increases diuresis/natriuresis while promoting myocardial relaxation and preventing remodeling. Natriuretic peptides also provide additional RAAS blockade. This compound was validated in the landmark PARADIGM-HF trial, in which the investigators studied symptomatic HFrEF whom had elevated plasma natriuretic peptides, or if they had a recent hospitalization with a GFR (eGFR) greater or equal to 30 mL/min/1.73 m^2 of body surface area. In this group, the combination of sacubitril/valsartan was superior to ACE inhibitors with a significant reduction in HF progression, HF-related hospitalizations, cardiovascular mortality, and overall mortality [58•].

In addition to continuing the therapies initiated during stage A and B, e.g., ACE inhibitors or ARB and Beta blockers, mineralocorticoid receptor antagonist (MRA), specifically aldosterone receptor blockade (spironolactone and eplerenone) have been proven beneficial for further neurohormonal blockade. In HFrEF patients with NYHA III-IV symptoms, MRA have reduced morbidity and mortality. NYHA class II HF patients with a history of a prior cardiovascular hospitalization or elevated BNP have a survival benefit from MRAs. MRAs should be avoided if the estimated glomerular filtration rate < 30 mL/min/1.73 m^2 or potassium greater than 5.0 mEq/L [59–61]. Post-acute MI patients with left ventricular dysfunction, whom developed HF symptoms or have history of diabetes mellitus, also gain a survival benefit from MRAs [62].

Prior to ACE inhibitors and ARBs, a combination of hydralazine and isosorbide dinitrate was one of the oldest strategies for HF treatment dating back to 1986 with the V-HEFT-1 trial. HFrEF patients who are not on an ACE inhibitor or ARB should be treated with this combination of vasodilators [63]. The A-HEFT trial found that African-American patients with NYHA class III-IV HFrEF gain a survival benefit from the addition of hydralazine and isosorbide dinitrate to a regimen containing an ACE inhibitor and beta blocker [64].

In stage C HF, the placement of an ICD is reasonable to prevent sudden cardiac death in both ischemic and non-ischemic patients, who are at least 40 days post-MI with an LVEF less than 35% with NYHA class II-III symptoms who are on the appropriate medical therapy with a life expectancy greater than 1 year [7]. In selected patients, cardiac resynchronization therapy (CRT), in which both the left and right ventricle are paced in synchrony to promote cardiac performance, improve symptoms, and reduce morbidity and mortality. Patients with an LVEF less than 35%, with a chronic left bundle branch block (LBBB) with QRS duration greater than 150 ms with NYHA class II-IV symptoms, are most likely to benefit from CRT. Other patients that may benefit from CRT are patients with non-LBBB with QRS duration greater than 150 ms, patients with QRS duration of 120 to 149 ms (with or without a LBBB), and HF patients with atrial fibrillation whom atrioventricular nodal ablation or pharmacological rate control induces near 100% ventricular pacing [7]. CRT is not beneficial in patients with narrow QRS [65].

For some stage C HFrEF patients, their resting heart rates continue to remain greater than 70 bpm, despite the beta

blockers being titrated to the maximum tolerate dose. Ivabradine is a new therapeutic medication which takes advantage of blockade of the sodium *If* current within the sinoatrial node, lowering the heart rate. Ivabradine in a recent randomized control trial found that HFrEF patients with NYHA class II-IV symptoms had a reduction in HF hospitalizations, though no survival benefit was elicited [26••, 66].

HFpEF Patients

Despite the amount of emerging data over the past decade, there still remains limited positive data on treatment strategies and thus limited recommendation from professional societies for HFpEF patients. It remains that the main treatment strategy for this patient population involves treating and minimizing exposure to the underlying etiology of the HFpEF. Systemic hypertension is a major cause of HFpEF and thus should be controlled to contemporary guidelines. Adequate relief of symptoms due to volume overload is often achieved with diuretics. As with HFrEF, coronary revascularization of patients with coronary artery disease is beneficial if there is proven ischemia or recurrent angina present. At this time, there are no medications that have proven to decrease mortality in HFpEF patients; however, two groups' of medications that influence the renin-angiotensin-aldosterone system may decrease hospitalizations. Results from the CHARM-Preserved trial show that in HFpEF patients with NYHA II-IV symptoms, ARBs, specifically candesartan, may modestly decrease the rate of HF-related hospitalizations; however, no survival benefit was demonstrated [67].

In the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) trial, MRAs may also decrease HF-related hospitalizations. The combined endpoint of CV and all-cause mortality was not statistically significant despite a decrease in HF-related hospitalizations; however, one criticism was the unusual amount of regional variation in this trial. Based on post hoc analysis, HFpEF patients with elevated BNP levels, or an HF admission within 1 year, an estimated glomerular filtration rate > 30 mL/min, creatinine < 2.5 mg/dL, and potassium < 5.0 mEq/L may benefit from the decreased rate of HF-related hospitalizations [68, 69].

Nitrates have been shown to be beneficial in certain HFrEF patients through reducing pulmonary vascular congestion and improving exercise tolerance. In the Nitrate's Effect on Activity Tolerance in Heart Failure With Preserved Ejection Fractions or NEAT-HFpEF trial, the investigators wanted to test if nitrates would provide any positive outcome data on HFpEF patient's. Unfortunately, long-acting nitrates did not demonstrate any survival benefit, quality of life, exercise tolerance, or NT-proBNP levels [70•]. Phosphodiesterase-5 inhibition, which upregulates cGMP activity, augmenting to nitric oxide system also failed to show any improvement in exercise tolerance in the Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction trial (RELAX trial) [71].

As mentioned earlier, treatment of systemic hypertension is a crucial part of the management of HF patients. In both stage C HFrEF and HFpEF patients, hypertension should be treated to achieve a systolic blood pressure goal of less than 130 mmHg. For HFpEF patients specifically, if hypertension persists despite adequate control of volume, additional oral antihypertensive should be added. Though there is limited data supporting which group of antihypertensives is more beneficial, it is believed that renin-angiotensin-aldosterone blockade may be the preferred first choice [26••].

There are many proven nonpharmacological interventions that are beneficial in stage C HFrEF patients [72–74]. Providing patients with education on HF to patients with the goal of self-care is strongly recommended. Exercise training is also safe and recommended to improve functional status. This could be achieved through a scheduled cardiac rehabilitation [75–77]. Salt restriction may be beneficial in stage C patients to reduce congestive symptoms. Recently, there two approaches to telemedicine that have been shown to improve clinical outcomes of HF patients, one is the CardioMems system which remotely monitors pulmonary artery pressures and the IN-TIME approach which uses multivariable monitoring through the ICD [78, 79].

Stage D HF

When the management of a stage C patient becomes refractory to maximum goal-directed medical therapy, progressing towards cardiogenic shock, advanced HF therapies need to be considered. These patients are referred to as stage D. To simplify the recognition of a patient in whom advanced therapies should be considered, Russell et al. described looking at the following: two or more ED visits or hospitalizations for the past year, progressive deterioration of renal function, cardiac cachexia, intolerance of goal-directed medical therapies (e.g., Hypotension), persistent or refractory hypotension (systolic blood pressure < 90 mmHg, inability to perform activities of daily living (NYHA III or IV), frequent need for escalation of diuretic doses, hyponatremia, and frequency of ICD firings [32••, 80]. In addition to continuing the same management as established in stage C HF patients, further efforts will need to be performed to maintain systemic perfusion and end-organ performance. Short-term intravenous inotropic support should be initiated until resolution of the acute precipitating problem for the ADHF has resolved or a definitive therapy has been achieved. Definitive therapies range from coronary revascularization, either percutaneously or surgically, mechanical circulatory support (MCS), or heart transplant. If the topic has

not already been broached with the patient, palliative and end of life care options should be discussed as this will help with a decision for definitive therapies [32••].

Ideally, inotropic support should be temporary until the patient transitions to a definitive therapy, however if the patient is not eligible for MCS or transplant, long-term intravenous inotropic support may be considered if required to manage symptoms adequately [81–85]. Definitive therapy could come in the form of temporary or durable MCS or transplant. MCS can be used to provide supplemental support by unloading the failing ventricle, promoting systemic perfusion. Temporary or nondurable MCS includes both percutaneous or extracorporeal options that may be used for left or biventricular support, while permanent implantable left ventricular assist device (LVAD) or biventricular assist devices (BIVAD) are referred to as durable MCS. There are a few strategies that will determine what definitive therapy to select. If cardiac recovery is anticipated, temporary or nondurable MCS could be used as a "bridge to recovery." If the hemodynamic compromise is too profound, temporary or nondurable MCS could be used as a "bridge to decision" until stability is achieved allowing for a full evaluation for possible transplant or durable MCS. Durable MCS could prolong survival in carefully selected patients until transplant can be performed, which is the ideal treatment for stage D patients [86–90]. If ineligible for cardiac transplant, a "destination therapy" strategy in which durable MCS for lifelong LVAD therapy use may be an option in select patients [32••, 91]. Despite limited availability of long-term outcome data, 2–3-year survival patients receiving continuous flow durable MCS is similar to early survival after heart transplant [32••]. The main weaknesses that affect long-term survival to durable MCS involve bleeding complications, thromboembolism, pump thrombosis, driveline infection, and device failure [92].

Postoperative right ventricular failure is another major linchpin, outside of pump complications. A thorough evaluation of right ventricular function prior to surgery is imperative as right ventricular failure increases perioperative mortality for both durable MCS and transplant. For those at high risk for persisting right ventricular failure after LVAD implantation or with chronic biventricular failure, implantation of a BIVAD may be necessary; however, BIVAD is not suitable for destination therapy as the outcomes for BIVADs are inferior to LVAD therapy, and thus diligence is required to screen for appropriate patients prior to development of right ventricular dysfunction [32••].

The INTERMACS scoring system is used for both prognostic evaluation and assisting what type of MCS is appropriate. In addition to this, the Survival After Veno-arterial ECMO (SAVE) scoring system could help predict survival in patient receiving ECMO support for cardiogenic shock [93•]. Data supporting percutaneous MCS over intraaortic balloon pump is limited; however, in meta-analysis of three randomized controlled trials, percutaneous MCS appeared as a safe option though no survival benefit was established [94•, 95].

The main challenges faced in cardiac transplantation other than donor organ shortage are the complications from long-term immunosuppression and graft rejection. Complications are not limited to cell-mediated or antibody-mediated rejections, transplant coronary artery vasculopathy, malignancy (particularly lymphomas and skin cancer), renal failure, and opportunistic infections. Well informed, motivated stage D patients with severe symptoms who are capable of complying with the intense postoperative course should be considered for transplant unless contraindicated. Transient or treatable contraindications should be considered prior to consideration of ineligibility. Examples of contraindications include active infections, pharmacologically irreversible pulmonary hypertension, active malignancy, systemic disease with multi-organ involvement or other co-morbidity with poor prognosis, current alcohol or drug abuse, or patients with poor social support. Durable MCS should be considered in patients with transient or treatable contraindications with subsequent reevaluation [32••].

Conclusion

Heart failure is a disease affecting millions of people worldwide [2]. We have briefly reviewed multiple definitions, etiologies as well as strategies on how to establish the diagnosis of heart failure and to initiate and optimize their treatments. While the prognosis for heart failure patients remains poor in comparison to other cardiovascular disease and even certain cancers, new advancements in therapy have shown survival and quality of life improvement.

Compliance with Ethical Standards

Conflict of Interest Jamael Hoosain, Jabar Whittier, Farhan Hasni, and Shelley Hankins declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Masoudi FA, Havranek EP, Smith G, et al. Gender, age, and heart failure with preserved left ventricular systolic function. J Am Coll Cardiol. 2003;41:217–23.

2. Liu L, Eisen HJ. Epidemiology of heart failure and scope of the problem. Cardiol Clin. 2014;32:1–8.
3. Mentz RJ, O'Connor CM. Pathophysiology and clinical evaluation of acute heart failure. Nat Rev Cardiol. 2016;13:28–35.
4. Mann DL, Zipes DP, Libby P, Bonow RO, Braunwald E. Braunwald's heart disease: a textbook of cardiovascular medicine, 10 edition. Philadelphia, PA: Elsevier/Saunders; 2015.
5. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European Society of Cardiology. Eur Heart J. 2012;33:1787–847.
6. Kane GC, Karon BL, Mahoney DW, et al. Progression of left ventricular diastolic dysfunction and risk of heart failure. JAMA. 2011;306:856–63.
7. Yancy CW, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. J Am Coll Cardiol. 2013;62:e147–239.
8. Ambrosy AP, Pang PS, Khan S, et al. Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: findings from the EVEREST trial. Eur Heart J. 2013;34:835–43.
9. Fonarow GC, Albert NM, Curtis AB, et al. Improving evidence-based care for heart failure in outpatient cardiology practices: primary results of the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF). Circulation. 2010;122:585–96.
10. O'Connor CM, Abraham WT, Albert NM, et al. Predictors of mortality after discharge in patients hospitalized with heart failure: an analysis from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). Am Heart J. 2008;156:662–73.
11. He J, Ogden LG, Bazzano LA, et al. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. Arch Intern Med. 2001;161(7):996–1002.
12. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure-lowering treatment. 6. Prevention of heart failure and new-onset heart failure—meta-analyses of randomized trials. J Hypertens. 2016;34(3):373–84.
13. Shore S, Grau-Sepulveda MV, Bhatt DL, et al. Characteristics, treatments, and outcomes of hospitalized heart failure patients stratified by etiologies of cardiomyopathy. JACC Heart Fail. 2015;3(11):906–16.
14. Mangini S, Higuchi ML, Kawakami JT, et al. Infectious agents and inflammation in donated hearts and dilated cardiomyopathies related to cardiovascular diseases, Chagas' heart disease, primary and secondary dilated cardiomyopathies. International Jour of Cardiology. 2015;178:55–62.
15. McNamara DM, Elkayam U, Alharethi R. Clinical outcomes for peripartum cardiomyopathy in North America. JACC. 2015;66(8):905–14.
16. Neck NS, Singh R, Vargova V, et al. Peripartum cardiomyopathy. World Heart Journal. 2014;6(2):139–47.
17. Mukku RB, Fonarow GC, Watson KE, et al. Heart failure therapies for end-stage chemotherapy-induced cardiomyopathy. J Card Fail. 2016;22(6):439–48.
18. Petretta M, Pirozzi F, Sasso L, et al. Review and metaanalysis of the frequency of familial dilated cardiomyopathy. Am Journal of Cardiology. 2011;108(8):1171–6.
19. Piano MR, Phillips SA. Alcoholic cardiomyopathy: pathophysiologic insights. Cardiovasc Toxicol. 2014;14(4):291–308.
20. Brack T, Randerath W, Bloch KE. Cheyne-Stokes respiration in patients with heart failure: prevalence, causes, consequences and treatments. Respiration. 2011;83:165.
21. Sweitzer NK, Lopatin M, Yancy CW, et al. Comparison of clinical features and outcomes of patients hospitalized with heart failure and normal ejection fraction (> or =55%) versus those with mildly reduced (40% to 55%) and moderately to severely reduced (<40%) fractions. Am J Cardiol. 2008;101:1151.
22. Drazner MH, Hellkamp AS, Leier CV, et al. Value of clinician assessment of hemodynamics in advanced heart failure: the ESCAPE trial. Circ Heart Fail. 2008;1:170.
23. Nohria A, Tsang SW, Fang JC, et al. Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure. J Am Coll Cardiol. 2003;41:1797.
24. Braunwald E. Biomarkers in heart failure. N Engl J Med. 2008;358:2148.
25. Taub PR, Daniels LB, Maisel AS. Usefulness of B-type natriuretic peptide levels in predicting hemodynamic and clinical decompensation. Heart Fail Clin. 2009;5:169–75.
26.•• Yancy CW, Jessop M, Bozkurt B, Butler J, Casey DE, Drazner MH, et al. ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Card Fail. 2017 Aug;23(8):628–651. **Latest set of American guidelines and recommendations on heart failure.**
27. Kim HN, Januzzi JL Jr. Natriuretic peptide testing in heart failure. Circulation. 2011;123:2015.
28.• Xin W, Lin Z, Mi S. Does B-type natriuretic peptide-guided therapy improve outcomes in patients with chronic heart failure? A systematic review and meta-analysis of randomized controlled trials. Heart Fail Rev. 2015;20:69–80. **A contemporary review on the use and potential benefit from a BNP-guided treatment strategy.**
29. Clerico A, Giannoni A, Vittorini S, et al. The paradox of low BNP levels in obesity. Heart Fail Rev. 2012;17:81–96.
30. Baggish AL, van Kimmenade RR, Januzzi JL Jr. The differential diagnosis of an elevated amino-terminal pro-B-type natriuretic peptide level. Am J Cardiol. 2008;101:43.
31. Martinez-Rumayor AA, Vazquez J, Rehman SU, et al. Relative value of amino-terminal pro-B-type natriuretic peptide testing and radiographic standards for the diagnostic evaluation of heart failure in acutely dyspneic subjects. Biomarkers. 2009;15:175.
32.•• Ponikowski P, Voors AA, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37:2129–200. **Latest set of European guidelines and recommendations on heart failure**.
33. Binanay C, Califf RM, Hasselblad V, et al. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. JAMA. 2005;294:1625–33.
34. Kahwash R, Leier CV, Miller L. Role of the pulmonary artery catheter in diagnosis and management of heart failure. Cardiol Clin. 2011;29:281.
35. Pfeffer MA, Braunwald E, Moye LA, et al. The SAVE investigators. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the survival and ventricular enlargement trial. N Engl J Med. 1992;327:669–77.
36. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med. 1987;316:1429–35.

37. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med. 1992;327:685–91.
38. Verdecchia P, Sleight P, Mancia G, et al. Effects of telmisartan, ramipril, and their combination on left ventricular hypertrophy in individuals at high vascular risk in the Ongoing Telmisartan Alone and in Combination with Ramipril Global Point Trial and the Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease. Circulation. 2009;120: 1380–9.
39. Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med. 2003;349:1893–906.
40. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction inpatients with left-ventricular dysfunction: the CAPRICORN randomized trial. Lancet. 2001;357:1385–90.
41. Vantrimpont P, Rouleau JL, Wun CC, et al. SAVE investigators. Additive beneficial effects of beta-blockers to angiotensin-converting enzyme inhibitors in the Survival and Ventricular Enlargement (SAVE) Study. J Am Coll Cardiol. 1997;29:229–36.
42. Exner DV, Dries DL, Waclawiw MA, et al. Beta-adrenergic blocking agent use and mortality in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a post hoc analysis of the studies of left ventricular dysfunction. J Am Coll Cardiol. 1999;33:916–23.
43. Australia-New Zealand Heart Failure Research Collaborative Group. Effects of carvedilol, a vasodilator-beta-blocker, in patients with congestive heart failure due to ischemic heart disease. Circulation. 1995;92:212–8.
44. The Beta-Blocker Evaluation of Survival Trial Investigators. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. N Engl J Med. 2001;344:1659–67.
45. Poole-Wilson PA, Swedberg K, Cleland JG, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. Lancet. 2003;362:7–13.
46. Fagerberg B, et al. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERITHF). Lancet. 1999;353(9169): 2001–7.
47. Scirica BM, Morrow DA, Cannon CP, et al. Intensive statin therapy and the risk of hospitalization for heart failure after an acute coronary syndrome in the PROVE IT-TIMI 22 study. J Am Coll Cardiol. 2006;47:2326–31.
48. Ho JE, Waters DD, Kean A, et al. Relation of improvement in estimated glomerular filtration rate with atorvastatin to reductions in hospitalizations for heart failure (from the Treating to New Targets [TNT] study). Am J Cardiol. 2012;109:1761–6.
49. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, et al. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med. 2011;364:797–805.
50. Grosskopf I, Rabinovitz M, Rosenfeld JB. Combination of furosemide and metolazone in the treatment of severe congestive heart failure. Isr J Med Sci. 1986;22:787–90.
51. Channer KS, McLean KA, Lawson-Matthew P, et al. Combination diuretic treatment in severe heart failure: a randomised controlled trial. Br Heart J. 1994;71:146–50.
52. Rosenberg J, Gustafsson F, Galatius S, et al. Combination therapy with metolazone and loop diuretics in outpatients with refractory heart failure: an observational study and review of the literature. Cardiovasc Drugs Ther. 2005;19:301–6.
53. Giamouzis G, Butler J, Starling RC, et al. Impact of dopamine infusion on renal function in hospitalized heart failure patients: results of the Dopamine in Acute Decompensated Heart Failure (DAD-HF) Trial. J Card Fail. 2010;16:922–30.
54. Elkayam U, Ng TM, Hatamizadeh P, et al. Renal vasodilatory action of dopamine in patients with heart failure: magnitude of effect and site of action. Circulation. 2008;117:200–5.
55. Costanzo MR, Guglin ME, Saltzberg MT, et al. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. J Am Coll Cardiol. 2007;49:675–83.
56. Ghali JK, Koren MJ, Taylor JR, et al. Efficacy and safety of oral conivaptan: a V1A/V2 vasopressin receptor antagonist, assessed in a randomized, placebo-controlled trial in patients with euvolemic or hypervolemic hyponatremia. J Clin Endocrinol Metab. 2006;91: 2145–52.
57. Schrier RW, Gross P, Gheorghiade M, et al. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. N Engl J Med. 2006;355:2099–112.
58.• McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. PARADIGM-HF investigators and committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371:993–1004. **Landmark trial highlighting the survival benefits of Angiotensin-neprilysin inhibitors.**
59. Pitt B, Zannad F, Remme WJ, et al. Randomized Aldactone Evaluation Study investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med. 1999;341:709–17.
60. Zannad F, McMurray JJ, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med. 2011;364: 11–21.
61. Vizzardi E, D'Aloia A, Giubbini R, et al. Effect of spironolactone on left ventricular ejection fraction and volumes in patients with class I or II heart failure. Am J Cardiol. 2010;106:1292–6.
62. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med. 2003;348:1309–21.
63. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure: results of a Veterans Administration Cooperative Study. N Engl J Med. 1986;314:1547–52.
64. Carson P, Ziesche S, Johnson G, et al. Vasodilator-Heart Failure Trial study group. Racial differences in response to therapy for heart failure: analysis of the vasodilator-heart failure trials. J Card Fail. 1999;5:178–87. **180**
65. Taylor AL, Ziesche S, Yancy C, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. N Engl J Med. 2004;351:2049–57.
66. Ruschitzka, et al. Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. N Engl J Med. 2013 Oct 10;369(15): 1395–405.
67. Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet. 2010;376:875–85.
68. Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet. 2003;362: 777–81.
69. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med. 2014;370: 1383–92.
70.• Pfeffer MA, Claggett B, Assmann SF, et al. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial. Circulation. 2015;131:34–42. **A recent landmark trial highlighting the potential benefit of aldosterone antagonism in HFpEF patients.**

71. Redfield MM, Anstrom KJ, Levine JA, et al. Isosorbide mononitrate in heart failure with preserved ejection fraction. N Engl J Med. 2015;373:2314–24.
72. Redfield MM, Chen HH, Borlaug BA, et al. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. JAMA. 2013;309:1268–77.
73. Boren SA, Wakefield BJ, Gunlock TL, et al. Heart failure self-management education: a systematic review of the evidence. Int J Evid Based Healthc. 2009;7:159–68.
74. Koelling TM, Johnson ML, Cody RJ, et al. Discharge education improves clinical outcomes in patients with chronic heart failure. Circulation. 2005;111:179–85.
75. Riegel B, Moser DK, Anker SD, et al. State of the science: promoting self-care in persons with heart failure: a scientific statement from the American Heart Association. Circulation. 2009;120:1141–63.
76. Davies EJ, Moxham T, Rees K, et al. Exercise training for systolic heart failure: Cochrane systematic review and meta-analysis. Eur J Heart Fail. 2010;12:706–15.
77. O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA. 2009;301:1439–50.
78. Austin J, Williams WR, Ross L, et al. Five-year follow-up findings from a randomized controlled trial of cardiac rehabilitation for heart failure. Eur J Cardiovasc Prev Rehabil. 2008;15:162–7.
79. AbrahamWT APB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW, Strickland W, et al. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. Lancet. 2011;377:658–66.
80. Hindricks G, Taborsky M, Glikson M, Heinrich U, Schumacher B, Katz A, et al. Implant-based multiparameter telemonitoring of patients with heart failure (IN-TIME): a randomised controlled trial. Lancet. 2014;384:583–90. **631**
81. Russell SD, Miller LW, Pagani FD. Advanced heart failure: a call to action. Congest Heart Fail. 2008;14:316–21.
82. O'Connor CM, Gattis WA, Uretsky BF, et al. Continuous intravenous dobutamine is associated with an increased risk of death in patients with advanced heart failure: insights from the Flolan International Randomized Survival Trial (FIRST). Am Heart J. 1999;138:78–86.
83. Hershberger RE, Nauman D, Walker TL, et al. Care processes and clinical outcomes of continuous outpatient support with inotropes (COSI) in patients with refractory endstage heart failure. J Card Fail. 2003;9:180–7.
84. Gorodeski EZ, Chu EC, Reese JR, et al. Prognosis on chronic dobutamine or milrinone infusions for stage D heart failure. Circ Heart Fail. 2009;2:320–4.
85. Packer M, Carver JR, Rodeheffer RJ, et al. The PROMISE study research group. Effect of oral milrinone on mortality in severe chronic heart failure. N Engl J Med. 1991;325:1468–75.
86. Oliva F, Latini R, Politi A, et al. Intermittent 6-month low-dose dobutamine infusion in severe heart failure: DICE multicenter trial. Am Heart J. 1999;138:247–53.
87. Trivedi JR, Cheng A, Singh R, Williams ML, Slaughter MS. Survival on the heart transplant waiting list: impact of continuous flow left ventricular assist device as bridge to transplant. Ann Thorac Surg. 2014;98:830–4.
88. Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term use of a left ventricular assist device for end-stage heart failure. N Engl J Med. 2001;345:1435–43.
89. Stevenson LW, Miller LW, Desvigne-Nickens P, et al. Left ventricular assist device as destination for patients undergoing intravenous inotropic therapy: a subset analysis from REMATCH (Randomized Evaluation of Mechanical Assistance in Treatment of Chronic Heart Failure). Circulation. 2004;110:975–81.
90. Rogers JG, Butler J, Lansman SL, et al. Chronic mechanical circulatory support for inotrope-dependent heart failure patients who are not transplant candidates: results of the INTrEPID trial. J Am Coll Cardiol. 2007;50:741–7.
91. Slaughter MS, Rogers JG, Milano CA, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med. 2009;361:2241–51.
92. Rose EA, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med. 2001;345(20):1435–43.
93.• Kirklin JK, Naftel DC, Pagani FD, Kormos RL, Stevenson LW, Blume ED, et al. Seventh INTERMACS annual report: 15,000 patients and counting. J Heart Lung Transplant. 2015;34:1495–504. **Large, contemporary study highlighting risk factors for mortality with continuous-flow pumps as well major causes and modes of death.**
94.• Schmidt M, Burrell A, Roberts L, Bailey M, Sheldrake J, Rycus PT, et al. Predicting survival after ECMO for refractory cardiogenic shock: the survival after veno-arterial-ECMO (SAVE)-score. Eur Heart J. 2015;36:1–11. **Recent study identified pre-ECMO factors which predict survival from refractory cardiogenic shock requiring ECMO and created a useful scoring system.**
95. Cheng JM, den Uil CA, Hoeks SE, van der Ent M, Jewbali LSD, van Domburg RT, et al. Percutaneous left ventricular assist devices vs. intra-aortic balloon pump counterpulsation for treatment of cardiogenic shock: a meta-analysis of controlled trials. Eur Heart J. 2009;30:2102–8.