Cardiology

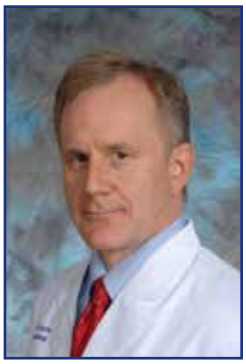
When failure is not an option

The war on heart failure — New drugs and devices in the arsenal

Rick Snyder, MD

Heart failure (HF) perhaps is one of the oldest and now one of the most prevalent diseases in human history. It is believed that the oldest identified case of decompensated HF was seen in the remains discovered in a plundered Egyptian tomb in the Valley of the Queens in 1904. The remains date back more than 3,500 years and were those of an Egyptian dignitary named Nebiri. Histological examination of the lungs in 2015 revealed pulmonary edema, likely due to heart failure. The Egyptians were not alone. Perhaps the oldest recorded example of HF was found in China. "The Yellow Emperor's Classic of Internal Medicine" discussed dropsical swellings as early as 2600 BC.

Today HF is endemic worldwide as the only cardiovascular disorder increasing in incidence and prevalence. Data from the American Heart Association Heart and Stroke Statistics Update 2014 show HF affects 2 percent of Western populations and more than 10 percent of people over age 70, reflecting the high prevalence of risk factors in this age group. Consequently, it is not surprising that HF is the most common cause of hospitalization in the elderly. Ominously, one out of five people over age 40 will develop HF. Current numbers show that 5.1 million Americans over age 20 have HF, and more than 650,000 cases are diagnosed annually.



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The growth of HF is explosive. The prevalence is expected to increase 46 percent between 2012 to 2030, resulting in more than 8 million people over age 18 with the disease. What's more, 5 to 10 percent of these patients represent the most severe form of HF — end-stage D — with the number of those who meet indication for a heart transplant conservatively estimated at more than 100,000. The direct and indirect costs for HF in the United States in 2012 were about $30.7 billion. Clearly, this disease demands attention from the broad medical and governmental healthcare communities.

The Basics

To best address HF from a prevention, diagnostic and treatment standpoint, a basic understanding of HF is crucial. Simply put, HF is a complex syndrome that results from a structural or functional impairment of ventricular filling or ejection of blood. The potential pathological insults that could result in HF consequently are extensive, diverse and prevalent, but are broadly categorized as ischemic and nonischemic, a useful pathologic designation that helps direct diagnosis and treatment. Despite a plethora of laboratory, noninvasive and invasive tests used in assessing a patient with possible HF, no single diagnostic test exists because HF largely is a clinical diagnosis based on a careful history and physical examination. The cardinal manifestations of HF are dyspnea and fatigue that limit exercise tolerance, and fluid retention, which may lead to pulmonary and/or splanchnic congestion and/or peripheral edema. Because some patients present without signs or symptoms of volume overload, the term "heart failure" is preferred over "congestive heart failure."

Classifications of Heart Failure

The American College of Cardiology/American Heart Association (ACC/AHA) staging system and the New York Heart Association (NYHA) functional classification provide complementary information about the presence and severity of HF.

ACC/AHA stages of HF, similar to the cancer staging system, emphasize the development and progression of disease, and can be used to describe individuals and populations.

Stage A and B groups represent patients who are just at risk for the syndrome of symptoms we call HF.

- **Stage A** reflects people who are at risk for HF but are without cardiac structural abnormalities or symptoms. Hypertension and lipid disorders should be controlled in accordance with contemporary guidelines. Likewise, other conditions that may lead to or contribute to HF, such as obesity, diabetes mellitus, tobacco use, and known cardiotoxic agents, should be controlled or avoided. Patients with atherosclerosis should be treated aggressively. This group will benefit most from efforts to identify and treat HF before the disease has begun to manifest. This is why ACC/AHA guidelines designate as Stage A this group of patients who are at risk of HF, although they do not have HF as a diagnosis.

- **Stage B** designates patients with structural heart disease but without prior or current signs or symptoms of HF. These patients commonly would have asymptomatic left ventricular systolic dysfunction and an EF (ejection fraction) of 40 percent. With Stage B patients, various types of structural

heart abnormalities are identified that can lead to Stage C symptoms and progressive deterioration in functional status and prognosis. The structural abnormalities include asymptomatic valvular disease, LVH with low EF, and previous myocardial infarction, all possibly resulting in left ventricular (LV) remodeling, and asymptomatic LV systolic dysfunction. Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) continue to form the foundation for those with a low EF, to prevent symptomatic HF. Evidence-based beta blockers (BB), carvedilol, metoprolol succinate, and bisoprolol continue to be indicated for the prevention of HF in those with asymptomatic low EF. If the etiology of the low EF were a history of acute coronary syndrome (ACS) or MI, then a mortality benefit emerges also for the ACEi, ARB and BB classes of drugs. Statins are indicated to prevent symptomatic HF in the MI and ACS group as well, irrespective of EF. Blood pressure should be controlled in those with LVH, according to contemporary guidelines. An ICD (implantable cardioverter defibrillator) is reasonable even in this asymptomatic group, in those with ischemic cardiomyopathy with an EF < 30 percent. Importantly, according to the medical dictum "First, do no harm," calcium channel blockers with negative inotropic effects may be harmful and should be avoided in asymptomatic patients with low EF.

- **Stage C** patients have structural heart disease and prior or current symptoms. HF is recognized as a progressive disease, frequently deteriorating into Stage D. The EF starts to become of primary importance in terms of prognosis and treatment decisions in the symptomatic Stage C and D groups.

- **Stage D** is end stage with refractory symptoms requiring specialized interventions. It is comprised of a broad group of symptomatic, medically refractory patients and ranges from the inability to carry on any activity of daily living to cardiogenic shock. It represents 5 to 10 percent of HF patients. The one-year mortality in this group ranges from 50 to 100 percent and is rivaled by a few known end-stage diseases, including most cancers and COPD. The specialized interventions used to treat this group include cardiac replacement therapy in the form of permanent ventricular assist devices and cardiac transplantation. Destination chronic IV inotrope medications such as milrinone and dobutamine have no real mortality benefit and, honestly, are reserved for palliation purposes in the setting of formal palliative care. In patients who are not candidates for VAD or transplantation, hospice plays just as prominent a role for the most advanced end-stage D HF patients as it does in end-stage cancer. The good news for cardiac transplantation recipients is that the median survival curve now is out to 12 years. In the permanent VAD space, two devices offer improvements in magnetic levitation design of the impellar and are beginning to address some of the deficiencies in VADs in terms of hemolysis, clotting and durability. VAD support out to five years is becoming more common. Promising innovations on the horizon include continued miniaturization of the device and percutaneous charging of the battery, which could permit removal of the drive line altogether and allow VAD therapy to take a quantum leap in cardiac replacement therapy.

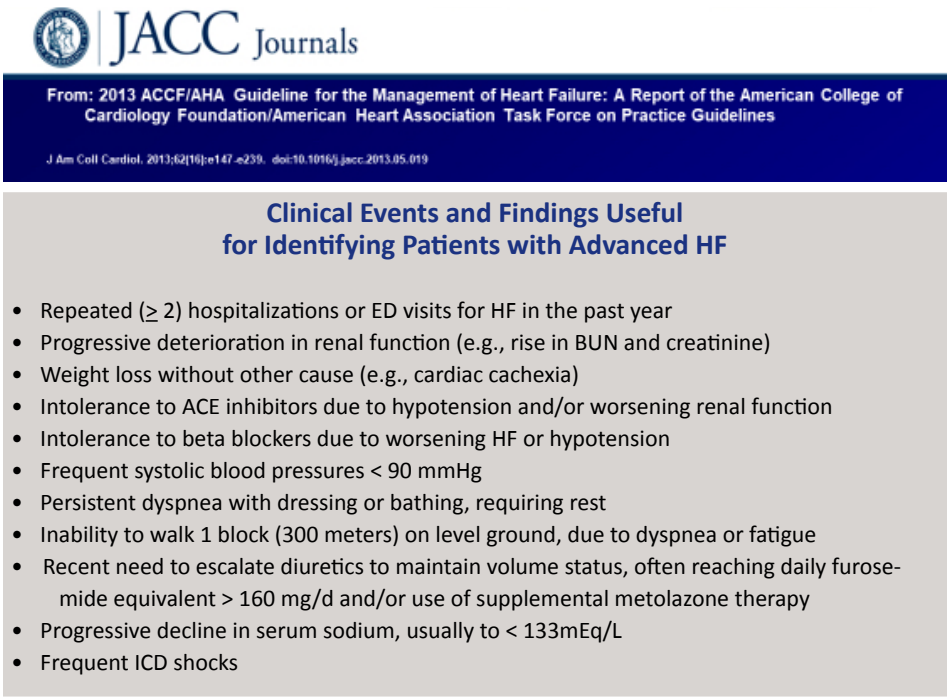

Figure 1

The main goal in the ongoing evaluation of patients with worsening HF is to identify when they have drifted into this prognostically poor medically refractory Stage D group before it is too late. Too often these patients are referred when they have become very ill and then are high risk or worse, no longer candidates for a VAD or transplant. The key question is when to refer for advanced HF therapy. The transition into advanced HF can be subtle, but specific clinical red flags help determine when a patient is becoming truly advanced and needs a referral to a board-certified advanced HF specialist.

Figure 1 is a comprehensive list of red flags to look for. One in particular is very predictive: HF admissions. Multiple HF admissions should be viewed as a cry for help for optimization of guideline-directed medical and device therapy, and an evaluation for advanced HF therapies in an advanced HF clinic.

An HF admission is an ominous event with an in-hospital mortality alone at 5 percent. Just one admission for HF predicts a median survival of 2.5 years, with each successive admission cutting the expected survival rate even more. For example, a second admission has a median survival of 1.5 years and by the time of the fourth admission, the median survival is less than a year. And if you throw CKD (GFR < 60ml/min/1.72m2— not a very high bar!) in the mix, you can cut those survival numbers by half! This is especially concerning when you realize that there are more than 1 million HF hospitalizations as a primary diagnosis each

year in this country, with 50 percent of those readmitted within six months. That means at least half a million people each year assume a median survival of 1.5 years simply because they experienced two HF hospitalizations. See Figure 2.

What we may consider a somewhat mundane HF admission is in reality an ominous event. Acute decompensated HF is no more a mere manifestation of worsening chronic HF than acute myocardial infarction is a mere worsening of stable angina. It is a seminal event in the downward progression of HF.

NYHA classes focus on exercise capacity and the symptomatic status of the disease. They are somewhat arbitrarily and subjectively defined according to the degree of impairment of ordinary physical activity:

Class I — no limitation of physical activity.

Class II — slight limitation.

Class III — marked limitation.

Class IV — the most serious class and a very broad class inclusive of those unable to carry on any activity without symptoms up to and including cardiogenic shock and imminent demise. This class carries a one-year mortality of 50 to 100 percent. This class paints the most accurate picture of current functional impairment and consistently has been the most powerful indicator of prognosis and treatment. For this reason, the ACC/AHA stage and NYHA functional class should be assessed for every HF patient at every outpatient encounter.

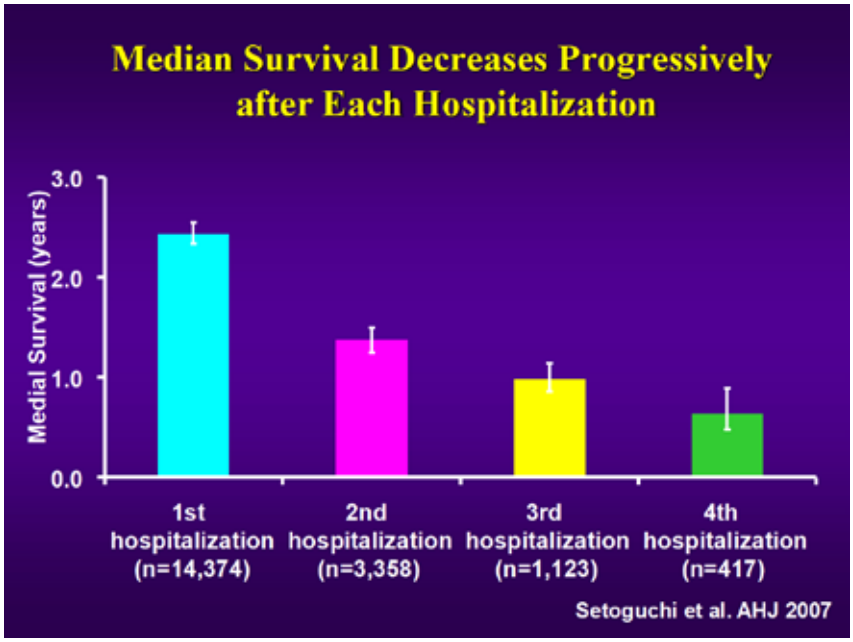

Figure 2

Pathological Abnormalities

The most frequently identified pathological abnormality involves the left ventricle and can be associated with a wide spectrum of abnormalities that ranges from patients with normal LV size and preserved ejection fraction to those with severe dilatation and/or markedly reduced EF. The EF is important in classification of HF because of differing demographics, comorbid conditions, prognosis, and response to therapies, and because most clinical trials select patients based on EF. Because of this, the classification of HF as HF*r*EF — Heart Failure reduced Ejection Fraction (sounds like "HEF-REF") and HF*p*EF — Heart Failure preserved Ejection Fraction (sounds like "HEF-PEF") are essential in the guidelines and frequently find themselves in cardiology specialists' consultative notes. HF*r*EF generally is defined as HF syndrome with an EF ≤ 40 percent and HF*p*EF as HF syndrome with an EF ≥ 50 percent. HF*r*EF and HF*p*EF each makes up about half of the overall HF burden, phenotypically look almost identical, and can be difficult to distinguish without an imaging modality to assess EF. The morbidity, readmission rate and mortality are similar, although perhaps marginally better in HF*p*EF. To make things a bit more complicated, the guidelines recognize a third category— HF*b*EF-HF borderline EF (EF 41 to 49 percent) which could reflect an early HF*r*EF state or an improved HF*r*EF condition, perhaps in response to medical therapy.

Treatment Guidelines

Treatment of HF bifurcates strongly according to EF classification lines. The vast majority of data and drug and device treatments are clustered under the HF*r*EF (< 40 percent) category. The treatment guidelines for HF*p*EF are shamefully few, despite having a similar prevalence, morbidity and mortality to that of HF*r*EF. So, let's start with the paltry recommendations found for HF*p*EF.

Recommendations for HF*p*EF. The hemodynamic perturbations of HF*p*EF largely reflect a disorder of ventricular filling in diastole. From a risk factor and epidemiological standpoint, it is associated with hypertension, atherosclerosis and obesity, and afflicts women more than men, especially in their golden years. The Class I recommendations are shockingly just two: Control the blood pressure in accordance with clinical practice guidelines and control volume overload with diuretics, both to prevent morbidity. The other recommendations are Class II (reasonable, may consider) or Class III (do not do!). These include revascularization for symptomatic coronary disease if felt to be contributing to HF, control of afib, and the specific use of an ACEi or ARB as it may be helpful for hypertension. Pretty vanilla, if you ask me.

The 2017 update includes the use of aldosterone receptor antagonists in HF*p*EF patients with an EF ≥ 45 percent, elevated BNP levels, or an HF admission in one year as something that may be considered to decrease hospitalizations. But it carries only a Class IIB level of support. Pretty weak! Class III ("do not do" indications) include nutritional supplements, nitrates and phosphodiesterase inhibitors. Shockingly, there are NO mortality benefit treatment indications for HF*p*EF. We have a lot of work to do for this group, gang.

Recommendations for HF*r*EF. A plethora of drugs and devices is indicated for HF*r*EF, with multiple large randomized controlled trials and the strongest levels of evidence addressing morbidity and mortality. The hardest evidence centers on inhibition of the renin-angiotensin-aldosterone and adrenergic systems. Most of these are well-known and established according to GDMT (guideline-directed medical therapy) in clinical practice. The drugs now are the well-ingrained generics ACEi, ARB and aldosterone receptor blocker classes, and guideline-directed beta

blockers. These drugs and devices (ICDs and pacemakers) have had a huge impact on morbidity and mortality from this disease in the HF*r*EF group.

New Drug Therapies and Devices

Despite successes of medications and devices in HF patients, HF remains a progressive disease with the need for continued new therapies and diagnostic modalities. In the last few years, two drug therapies have emerged for HF*r*EF patients that improve their quality of life and mortality.

Entresto. Entresto is a combination pill composed of the angiotensin receptor blocker valsartan and a new inhibitor of the powerful enzyme neprilysin called sacubitril. This pill represents a new class of medication referred to as ARNI. In ARNI, an ARB is combined with an inhibitor of neprilysin, an enzyme that degrades natriuretic peptides; bradykinin; adrenomedullin; and other vasoactive peptides. Neprilysin activity is increased in HF and has adverse prognostic significance. Neprilysin inhibition is the next neurohumoral frontier in the treatment of HF. In the Paradigm-HF trial that compared the first approved ARNI — valsartan/sacubitril — with enalapril in symptomatic patients with HF*r*EF tolerating an adequate dose of ACE inhibitor or ARB, the ARNI reduced the composite endpoint of cardiovascular death or HF hospitalization by 20 percent. So overwhelming was the clinical benefit in this trial that the study was ended early. So powerful was the statistical significance in this trial that the p value had 6 zeros ($P < 0.0000004$). The benefit was seen to a similar extent for both death and HF hospitalization, and was consistent across subgroups.

The use of ARNI is associated with the risk of hypotension and renal insufficiency and may lead to angioedema. Based on the strength of this trial involving 8,442 patients with an EF < 40 percent, with symptomatic HF, it now carries a Class I indication on par with ACEi and ARBs. The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors (Level of Evidence: A), OR ARBs (Level of Evidence: A), OR ARNI (Level of Evidence: B-R) in conjunction with evidence-based beta blockers, and aldosterone antagonists in selected patients is recommended for patients with chronic HF*r*EF to reduce morbidity and mortality. It should not be used in patients with a history of angioedema, or concomitantly with an ACEi, or within 36 hours of the last dose.

Corlanor. The other new useful drug representing a new class is ivabradine, sold as Corlanor. Ivabradine is a therapeutic agent that selectively inhibits the I_f called the *funny* channel current in the sinoatrial node, reducing heart rate. It is theorized that one benefit of beta blockers in HF patients is reducing the heart rate to less than 70 bpm, rather than its negative inotropic effect. The downside to beta blockers in HF is that their use may be limited by how much they lower the blood pressure, which adversely impacts contractility. Hence, their use frequently is limited and the achievable doses are not in line with those that demonstrated benefit in the landmark trials. This would not be a problem with this new class of drugs which impacts only the SA node and the rate of depolarization, and thus does not have a significant negative impact on contractility or blood pressure.

One randomized controlled trial demonstrated the efficacy of ivabradine in reducing the composite endpoint of cardiovascular death or HF hospitalization. The study included patients with HF*r*EF (NYHA class II-IV, albeit with only a modest representation of NYHA Class IV) and left ventricular ejection fraction (LVEF) < 35 percent, in sinus rhythm with a resting heart rate of 70 bpm. The target of the drug is to reduce the resting heart rate. It carries an IIa indication — reasonable to do, according to the following guideline: Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA Class II-III) stable chronic HF*r*EF (LVEF ≤ 35 percent) who are receiving guideline-directed evaluation and management, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest.

Other guidelines from the 2017 update in the HF*r*EF group emphasize the need to control blood pressure to less than 130/80, and to avoid adaptive servo-ventilation for central sleep apnea which has been determined to cause harm.

Digoxin. Notably absent from Class I indications for HF is digoxin. Digitalis was the go-to HF drug ever since William Withering described the medicinal uses of the foxglove plant in dropsy in 1785. More recent data from multiple large randomized trials have been disappointing and failed to demonstrate a mortality benefit. These studies have resulted in a reduction of the role of digoxin to decreasing hospitalizations for HF, a use for which it carries a modest IIa indication. It now is viewed as the fourth or fifth drug to use in an HF patient.

Diagnostic devices. Diagnostic device modalities are beginning to emerge and have an impact on HF. The Cardiomems HF monitor is one such device. The monitor, about the size of a dime, is implanted in the pulmonary artery via a catheter from the femoral vein. It is indicated for wirelessly measuring and monitoring pulmonary artery pressure and heart rate in NYHA Class III HF patients who have been hospitalized for heart failure in the previous year. Physicians use the hemodynamic data for heart failure management with the goal of reducing heart failure hospitalizations. The first and only FDA-approved heart failure monitor proven to significantly reduce heart failure hospital admissions and improve quality of life, the Cardiomems monitor has been proven to reduce hospital admissions by 33 percent over an average of 18 months. Although its use is included in the European cardiology guidelines, it has not made much penetration in the US market due to lack of inclusion in US cardiology guidelines and National Coverage Determination resistance from CMS.

Despite the expanding arsenal of "shock and awe" wonder drugs and devices that we can employ in the war on heart failure, the greatest missed opportunities still are the failures to use these very drugs and devices to their optimal guideline-directed potential in the first place. Far too often we fail to optimally titrate HF drugs to their guideline-directed doses, or, worse yet, not at all. Far too many times we fail to utilize resynchronization device therapy and attempt rehabilitation of a failing ventricle. And far too many times we fail to refer a deteriorating patient for evaluation of advanced HF therapies until it is too late. Properly addressing these types of endemic failures will have the greatest benefit to our HF patients. **DMJ**