End-of-Life Options for Patients with Advanced Heart Failure

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Abstract Heart failure is a progressive disease with significant morbidity and mortality, but prognostication often is difficult. Many of the evidence-based therapies for heart failure provide symptomatic benefit, but may have intolerable side effects for patients with advanced disease. At the end of life, there is evidence of varying strengths for pharmacologic and nonpharmacologic relief of common symptoms like dyspnea, fatigue, pain, and depression. Patients also may benefit from inotropic therapy, ventricular assist devices, and hospice care. It is important for physicians to encourage patients to formulate advance directives, including decisions about do not resuscitate orders and deactivation of implantable cardioverter-defibrillators and ventricular assist devices.

Keywords Heart failure • Palliative care • Hospice • Inotropic therapy • Brain natriuretic peptide • Ventricular assist device • Implantable cardioverter-defibrillator • ICD deactivation • Cardiac resynchronization therapy • Advance directives • Do not resuscitate order

Introduction

Heart failure (HF) currently affects more than 5 million Americans, and, unlike other forms of cardiovascular disease, prevalence is rising. After diagnosis, 1-year mortality is 1 in 5, with a six- to ninefold increased risk of sudden cardiac death [1]. Roughly 5% of patients with HF worldwide have end-stage disease that is refractory to conventional medical management. Only a minority of these end-stage patients are young enough, healthy enough, and have the requisite social support to be eligible for a heart transplant; of those who are eligible, only a fraction will receive a heart. The patients who continue to live with HF have worse quality of life and higher rates of depression, pain, dyspnea, and fatigue [2, 3]. The focus of this article will be options for patients and their caregivers to improve the quality of life, as well as the “quality of death.” Advanced therapies, such as heart transplantation, may be appropriate for a small selection of patients but are beyond the scope of this article.

Prognostication: Identification of the End-Stage Patient

HF is a progressive chronic disease that is generally characterized by acute exacerbations superimposed on a more gradual decline [4]. However, for many patients, the trajectory of disease takes a more variable pattern.

Because of the variability in disease trajectory, it is notoriously difficult to prognosticate in HF. Determining prognosis is critical in establishing when patients may be appropriate for advanced therapies, such as cardiac transplantation and mechanical circulatory support. Furthermore, if a physician certifies that a patient has fewer than 6 months to live and the patient agrees to forego curative or life-
prolonging medical treatments, the patient is eligible for the Medicare hospice benefit, which will cover the costs of care designed to maximize comfort and symptom control. Barriers to accurate prognosis can prevent or delay timely referrals to hospice and also can lead to aggressive, though futile, care at the end of life.

There are multiple predictive models to assist with estimating prognosis in HF [5–7]. The Seattle Heart Failure Model, available with online calculator, can help predict mortality at 1, 2, and 5 years. Assuming maximal medical management, other factors that can help physicians predict an increased likelihood of death include New York Heart Association (NYHA) class IV HF, frequent emergency department visits or hospitalizations, functional decline (Karnofsky score less than 50% or dependency in activities of daily living), unintended weight loss greater than 10% of total body weight, albumin less than 2.5 g/dL, severe left ventricular dysfunction with an ejection fraction less than 20%, symptomatic arrhythmia, prior cardiopulmonary resuscitation, prior syncope, embolic stroke, and concomitant HIV disease [8, 9]. Persistent elevation of brain natriuretic peptide also has been associated with a worse prognosis in advanced disease [10].

Even if patients do not qualify for the Medicare hospice benefit, they still may benefit from a palliative care consultation in either the inpatient or outpatient setting. Palliative care is a discipline that aims to relieve suffering, improve quality of life, and provide support to patients and the family members or friends who care for them. This requires a holistic approach that addresses the physical, emotional, spiritual, and logistical needs of patients and their caregivers. Palliative care improves outcomes, including increased patient and family satisfaction with care and improved symptom management, as well as patient well-being and dignity, communication with health care providers, emotional and spiritual support for patients and caregivers, and access to community support services [11–13].

Symptom Management for End-Stage Heart Failure

At all stages of disease, there are HF therapies both to decrease mortality and to ameliorate symptoms. Three classes of drugs, β-blockers [14], angiotensin-converting enzyme (ACE) inhibitors [15], and aldosterone antagonists [16], all have been shown to improve symptoms, decrease hospitalizations, and improve mortality. Digoxin decreases hospitalizations and may improve symptoms, but thus far has not been demonstrated to improve mortality [17]. Cardiac resynchronization therapy (CRT), also called biventricular pacing, is indicated for symptomatic patients with interventricular conduction delay and an ejection fraction less than 35%. CRT improves mortality, decreases HF symptoms and hospitalizations, and improves quality of life [18].

As disease progresses to end stage, patients commonly develop hypotension and renal disease. Hypotension may limit the use of β-blockers, ACE inhibitors, and aldosterone antagonists. Renal failure may limit the use of ACE inhibitors, aldosterone antagonists, and digoxin. When patients are admitted to the hospital with an acute decompensation, these medications are frequently held, or doses are reduced, because of hypotension or a worsening creatinine clearance. Often these medications are never restarted, either appropriately or inappropriately, despite improvements in blood pressure and renal function during the hospital stay or after discharge. With advanced HF, it is important to weigh the symptomatic or palliative benefits of medications against their adverse effects. For example, renal failure will limit diuretic use, leading to fluid overload and consequent dyspnea and fatigue.

There also is a role for nonpharmacologic treatments in symptom improvement [19]. However, these treatments rarely have been studied in HF specifically. More often, data were culled from studies of symptom management in patients with cancer or, less commonly, patients with chronic obstructive pulmonary disease (COPD). Here, we will explore the most common symptoms of HF: dyspnea (includes fluid retention), fatigue, pain, and depression. We then will describe the treatments that are supported by moderate to strong evidence and mention some treatments that are not evidence based or are contraindicated.

Dyspnea

This is the symptom of HF that is reported most often and has been studied most extensively. Pathogenesis is generally multifactorial, and may include volume overload and pulmonary congestion due to poor systolic function, as well as increased afterload. There is strong evidence for loop diuretics with or without thiazides in the management of breathlessness that is due to fluid retention [20]. Patients who develop increasing levels of diuretic resistance may benefit from aquapheresis [21]. There also is strong evidence for the use of low-dose opioids for dyspnea [22]. The doses required typically are a fraction of the doses required for analgesia, and tolerance to central nervous system side effects occurs in less than a week. Strong evidence supports the use of inotropes to improve perfusion [23]. There also is strong evidence for afterload reduction with long-acting nitroglycerin formulations such as isosorbide dinitrate, with or without the vasodilator hydralazine, but use of these medications may be limited by hypotension [24].

There is moderate strength of evidence for hawthorn extract [25], breathing training, chest wall vibration, neuro-
electrical muscle stimulation (extrapolated from studies of patients with COPD), and walking aids or rollators (extrapolated from studies of patients with COPD) [26].

There is inadequate or weak evidence for oxygen use in patients who are not hypoxic [27] and for the use of benzodiazepines, although they may help with symptoms of panic associated with dyspnea [26].

Fatigue

Strong evidence supports treating underlying causes of fatigue, like anemia or infection [28]. There also is strong evidence for exercise training [29] and pharmacologic stimulants like methylphenidate [30]. There is moderate strength of evidence to support oral use of hawthorn extract [25].

Pain

Strong evidence supports using opioids as first-line agents for moderate to severe pain of all types [31•]. Bone pain can be treated with bisphosphonates [31•]. Anginal pain can be treated with nitrates, ranolazine, or even intracoronary stenting in patients whose anginal pain does not improve with pharmacotherapy [32]. Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided due to the risk of gastrointestinal bleeding, renal failure, and fluid retention [21].

Depression

Depression is common in patients with HF [2]. There is strong evidence for different categories of antidepressants, including selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and tricyclic antidepressants [3]. There is moderate strength of evidence for exercise to treat depression [33]. There is only weak evidence for psychological interventions like cognitive behavioral therapy, counseling, or supportive therapy [34].

Inotropic Therapy

Inotropic agents, including dopamine, dobutamine, and milrinone, are effective for treating refractory symptoms of HF and can decrease hospitalizations. However, these agents do not improve survival, and actually may increase mortality [35, 36]. Because of concerns about the increase in mortality, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines classify intravenous inotropes as a class IIb indication for patients with end-stage HF with systolic dysfunction, hypotension, and low cardiac output or hypoperfusion [1]. Chronic infusions of intravenous inotropes never have been studied in large randomized controlled trials.

When deciding whether to initiate inotropes, patients and their family members should be involved in the decision-making process and should be informed that benefits are uncertain, that not all patients will have relief from congestion or fewer hospitalizations. Risks include sudden death, complications from the intravenous line, and the possibility of dependence on inotropic therapy [37]. Though not well studied, patients with defibrillators who are on inotropes likely will be at an increased risk for shocks, both appropriate and inappropriate. When patients are inotrope dependent and cannot be weaned, 1-year mortality is extremely high [38].

Some hospices, either inpatient or home based, provide intravenous inotrope therapy; however, cost considerations prevent many agencies from providing them [39]. In a recent study, both dobutamine and milrinone were associated with decrease in hospitalizations; dobutamine was overall cost saving at 1 year, while milrinone was significantly more costly than standard therapy [36].

Hospice

Hospice provides relief from pain and other symptoms, as well as spiritual and emotional support to patients and caregivers, either at home or in a homelike setting in a hospice program. Late referrals to hospice correlate with decreased family satisfaction, less satisfaction with hospice services, more unmet needs, lack of awareness about what to expect at time of death, and more concerns with coordination of care [40]. Hospice also leads to cost savings. Specifically, for patients with HF, enrollment in hospice resulted in a reduction in mean Medicare cost per patient from $53,528 to $46,792.37 [41]. This cost saving occurs despite the relatively short time most patients are in hospice. The mean length of stay is only about 2 months, and median length of stay was 20 days [42].

HF is the second most common hospice diagnosis (cancer is first). Cancer accounts for less than a quarter of the deaths each year in the United States, but cancer patients make up close to half of hospice patients. Patients with HF account for 11% to 12% of hospice patients [43, 44•]. Both patient factors and hospital factors are associated with likelihood of referral to hospice. Patients who were referred to hospice were older, had been admitted for decompensated HF in the previous 6 months, were more likely to receive intravenous inotropic therapy, were less likely to receive ACE inhibitors, and had low systolic blood pressure and renal failure. Hospitals that had higher adherence rates to quality indicators for HF were more likely to refer patients to hospice [43]. There also are racial
and ethnic disparities in hospice utilization; based on Medicare claims data, black and Latino patients are about half as likely to use hospice as white patients [44•].

Advance Directives

The physician should initiate end-of-life planning early in the relationship with the patient, when the patient is cognitively intact and able to state his or her wishes. It is helpful if the patient’s family members participate in these conversations, so they understand both that HF is a progressive and ultimately terminal disease and how their loved one wants to manage the disease when it becomes advanced. We have included a checklist for providers to use at each visit to help assess patients and to remind providers to begin and/or continue the ongoing discussion about advance directives (Fig. 1).

Do Not Resuscitate Orders

A patient with HF is 10 times less likely than a patient with AIDS or cancer to have a do not resuscitate (DNR) order, even when prognoses are similar [45]. Studies consistently show that most patients with HF prefer resuscitation. At the start of the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments trial, only 23% of patients with HF did not want to be resuscitated, and 2 months later, 40% of those changed their minds (at the 2-month follow-up, only 14% of those who initially wanted resuscitation changed their minds). In that trial, patients who did not want to be resuscitated were more likely to be older, had a perception of a worse prognosis and a life expectancy less than 2 months, had worse functional status, and had higher income. Despite having advanced disease, less than one fourth of these patients had discussed resuscitation with their physician [46]. The inpatient setting, where patients with HF often are acutely decompensated, may be an anxiety-provoking and ultimately inappropriate place to have a discussion about a DNR order [47]. The best environment would be an outpatient visit with a provider who knows the patient well.

It is unclear why patients with HF and their doctors are resistant to DNR orders. The waxing and waning trajectory of disease may play a role. Doctors may be concerned that a DNR order may limit their patient’s care; if this order precludes admission to an intensive care unit in a hospital where inotropes are only given in those units, the order stands in the way of appropriate care [47]. In one large multicenter trial, patients with HF with DNR orders were less likely to meet quality indicators for HF, including assessment of left ventricular function, use of ACE inhibitors or aldosterone antagonists, anticoagulation, or use of nonpharmacologic interventions, which raised the question of misinterpretation of the strict application of a DNR order to cardiac arrest [48•].

Deactivating Implanted Cardioverter-Defibrillators

Implanted cardioverter-defibrillators (ICDs) reduce mortality in patients with HF by decreasing sudden cardiac death due to arrhythmias [49]. As systolic function worsens, patients have more arrhythmias and are likely to receive more frequent shocks, which cause significant pain and anxiety [50] and are associated with worse quality of life [51•] and increased mortality [52•]. The ACC/AHA guidelines include a class I recommendation, based on C-level evidence, for physicians to discuss with their patients the option for ICD deactivation at the end of life [1]. Still, many clinicians do not address deactivation with their patients, and most devices remain active until death; patients receive shocks up until death [53]. Qualitative studies have shown that patients may not fully understand how ICDs work, which may contribute to reluctance to deactivate their devices [54•]. Qualitative studies with physicians showed that they regarded ICD deactivation as separate and distinct from other end-of-life planning, and so were more likely to address DNR orders than ICD deactivation [54•].

Most hospice programs do not have formal rules about ICDs. In a recent survey of 900 hospice programs, almost all admitted patients with ICDs, but only 10% had a policy that addressed deactivation. Nearly 6 out of 10 programs reported that a patient had been shocked in the past year. On average, 42% of patients with ICDs had the shocking function deactivated, and patients in hospices with a deactivation policy were almost twice as likely to have their device turned off when compared to patients in hospices with no formal policy [55•].

Before ICD implantation, doctors should discuss with patients the possibility of deactivation in the future. It is best if this dialogue occurs early while the patient is still capable of participating in the discussion. Patients should be reassured that deactivating an ICD will not result in immediate death and that the process of deactivation is not painful [55•]. The patient’s wishes should be documented clearly in the medical record.

Is There a Role for Deactivation of Cardiac Resynchronization Therapy?

CRT improves mortality and quality of life [18]. Because of this symptomatic benefit, the AHA recommends CRT for NYHA class III and IV HF, but not as salvage therapy in very advanced patients in whom the risks and discomfort of device placement may exceed the benefit they will derive
from ventricular synchrony. ICDs without CRT are contra-indicated for patients with NYHA class IV HF [56]. It may be appropriate to continue CRT for patients even when the decision has been made to turn off ICDs.

Ventricular Assist Devices

A ventricular assist device (VAD) is a battery-operated mechanical device that can be surgically implanted into either ventricle and consists of a blood pump that decreases the workload of the diseased ventricle. Mechanical circulatory support with a VAD can be used either as a bridge to cardiac transplantation or as destination therapy in patients who are not eligible for transplant. Since 2003, based on the survival and quality-of-life improvements reported in the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure trial [38], the Center for Medicare and Medicaid Services approved the use of VAD as destination therapy in patients who were not candidates for transplant. In January 2010, the HeartMate II (Thoratec Corporation, Pleasanton, CA) VAD became the first continuous-flow device approved for destination therapy.

Given improvements in technology and increases in the prevalence of HF, the use of VAD for treatment of HF is likely to increase significantly. The ACC/AHA guidelines cite level B evidence for a class IIa recommendation for a left ventricular assist device as destination therapy in patients with refractory end-stage HF and an estimated 1-year mortality of over 50% despite medical therapy [1]. When the physician begins to discuss implanting a VAD as

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**Fig. 1** Checklist for providers.

ACE angiotensin-converting enzyme; DNR do not resuscitate; EF ejection fraction; ICD implantable cardioverter-defibrillator; NYHA New York Health Association; VAD ventricular assist device

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**Step 1: Assess adherence to guideline-based therapy**

- Has left ventricular EF been assessed in the past 6–12 months?
- If EF less than 40%, is the patient taking a β-blocker?
- If EF less than 40%, is the patient taking an ACE inhibitor or angiotensin-receptor blocker?
- If EF less than 35%, is the patient taking an aldosterone antagonist?
- If EF less than 30%, does the patient have an implantable cardioverter-defibrillator?
- If EF less than 35%, does the patient have an intraventricular conduction delay (QRS > 120 ms) that may benefit from cardiac resynchronization therapy?

**Step 2: Assess functional status**

- Does the patient have symptoms at rest (NYHA Class IV)?
- Has this changed in the past 12 months?
- Does the patient require help often and require frequent medical care (Karnofsky score 50%)?

**Step 3: Assess markers of heart failure progression**

- How many visits to the emergency department in the past 12 months for decompensated heart failure?
- How many admissions to the hospital in the past 12 months for decompensated heart failure?
- How many medications been stopped or doses decreased due to low blood pressure, increase in creatinine, or other side effect? Can the medication be restarted today?
- Measure albumin if it has not been assessed in previous 6 months
- Measure brain natriuretic peptide level if it has not been assessed in previous 6 months
- Weigh the patient and assess for significant weight loss

**Step 4: Create advance directives**

- Do not resuscitate order; mention that DNR applies only to cardiac arrest
- If the patient has an ICD, is he or she aware that the ICD can be deactivated?
- Discuss with the patient scenarios where he or she might want the device turned off
- If the patient has a VAD, is he or she aware that the VAD can be deactivated?
- Discuss with the patient scenarios where he or she might want the device turned off

**Step 5: Establish plans for the future**

- Use Seattle Heart Failure Model to quantify prognosis
- Is the patient a candidate for orthotopic heart transplant? Refer to transplant center or begin evaluation for transplant
- Is the patient a candidate for VAD either as a bridge to transplant or for destination therapy? Begin evaluation for VAD
- Is the patient a candidate for hospice? Discuss with the patient why you think this is appropriate, and work with social workers to refer the patient to a home-based or facility-based hospice program, depending on his or her preferences and support at home
destination therapy, patients should be made aware of the common complications. They also should know that at the end of life, VAD mechanical dysfunction can lead to a sudden decrease in cardiac output and rapid decompensation. In other patients, the devices continue to function, possibly even after the patient is clinically brain dead, and may prolong the dying process. Before implantation, the patient, together with his or her family and doctor, should establish advance directives that outline conditions where he or she would want to turn off the VAD. Specifically, if the patient were permanently unable to interact with loved ones, would he or she want care focused on comfort or maximal prolongation of life? If he or she chooses comfort, the VAD would need to be turned off in that scenario. A patient who is receiving a VAD for destination therapy may benefit from increased palliation and hospice.

Conclusions

Despite progress, the prevalence of patients with HF continues to increase. Early identification of patients with end-stage disease facilitates their care, whether the patients are appropriate for heart transplant or mechanical circulatory support or are more appropriate for palliative therapies. Early identification also allows for timely discussions between patients and health care providers about advance care planning. These discussions should address patients’ preferences about resuscitation and, in appropriate patients, defibrillator deactivation. As patients decline, a gradual transition between life-saving therapies and comfort care measures is appropriate. The expanding use of VAD therapies may pose a unique challenge for health care providers at the end of life.

Disclosures No potential conflicts of interest relevant to this article have been reported.

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55. • Goldstein N, Carlson M, Livote E, Kutner JS: Brief communi- cation: Management of implantable cardioverter-defibrillators in hospice: A nationwide survey. Ann Intern Med 2010, 152:296–299. The authors surveyed hospices and found that while few had...
a formal policy in place to address ICD and deactivation, the existence of a formal policy was associated with an increase in device deactivation.