


Advanced heart failure with reduced ejection fraction

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ABSTRACT

Patients suffering advanced heart failure with reduced ejection fraction (HFrEF) account for a large portion of patients admitted to hospitals worldwide. Mortality and 30-day readmission rates for HFrEF are now a focus of value-based payment models, making management of this disease a priority for hospitals, physicians, and payers alike. Angiotensin-converting enzyme inhibitors have been the cornerstone of therapy for decades. However, with treatment, the prognosis for patients with advanced HFrEF remains poor. Fortunately, advances in medical therapy and mechanical support offer some patients improvement in both survival and quality of life. We review advances in short- and long-term mechanical support and explore changes to organ allocation for cardiac transplantation. In addition, we provide a guide to facilitate appropriate referral to an advanced heart failure team.

KEYWORDS Advanced heart failure; angiotensin receptor blocker; cardiac transplantation; extracorporeal membrane oxygenation; heart failure with reduced ejection fraction; left ventricular assist devices; neprilysin inhibition

CME

Target audience: All physicians

Learning objectives: After reading the article, the learner should be able to

1. Recognize the poor prognosis of patients with advanced heart failure
2. Distinguish between the different types of mechanical support used to treat patients
3. Select patients who would benefit from referral to advanced heart failure cardiologists

Faculty credentials/disclosure: Dr. Hicks is interim medical director of advanced heart failure, mechanical circulatory support, and cardiac transplant at Baylor Scott & White in Temple, Texas, and the assistant program director for the cardiology fellowship. Dr. Velazco is director of the cardiothoracic intensive care unit at Baylor Scott & White Medical Center – Temple. Dr. Gohar is medical director of the advanced heart failure and mechanical circulatory support service, Baylor All Saints Medical Center, Fort Worth, Texas. Dr. Seliem is a board-certified interventional cardiologist completing a heart failure fellowship at Baylor University Medical Center at Dallas. Dr. Hall is chief of transplant cardiology, mechanical circulatory

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Received November 18, 2019; Revised February 10, 2020; Accepted February 20, 2020.

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Expiration date: July 1, 2022.

In the United States, between 250,000 and 300,000 patients under the age of 75 have advanced heart failure, i.e., objective evidence of cardiac dysfunction, usually based on imaging, in conjunction with dyspnea and fatigue that limit physical activity.¹ Heart failure is progressive and the prognosis for advanced heart failure remains poor, with an annual mortality rate averaging 25% to 50%, on par with that of patients with pancreatic cancer.² Patients tend to be evenly divided between those with preserved ejection fraction and those with reduced ejection fraction (HFrEF). While few therapies exist for heart failure with preserved ejection fraction, cardiac transplantation remains the most effective treatment option for patients with HFrEF, with 1-year survival rates of 90%.³ Yet the supply of organs is limited. Left ventricular assist device (LVAD) therapy provides an important alternative to transplantation, offering 1-year survival rates of 80% and 2-year survival rates of 70%.⁴ However, misconceptions persist about which patients should and should not be referred for advanced therapies. Chief among these is a belief that HFrEF patients must be end-stage, New York Heart Association (NYHA) class IV, or near death to be considered for cardiac transplantation or advanced mechanical support.⁵ We review areas of progress in heart failure management and provide guidance on referral of HFrEF patients to the advanced heart failure team.⁶

MEDICAL THERAPY

It has been recognized for several decades that the renin-angiotensin-aldosterone system plays an important role in maladaptive responses that contribute to the morbidity and mortality of HFrEF. Along with sympathetic nervous system activation, renin-angiotensin-aldosterone system activation in HFrEF leads to increases in preload, worsening afterload, and left ventricular remodeling. Angiotensin-converting enzyme inhibitors (ACEIs), beta-blockers, and aldosterone antagonists are long-standing and well-recognized mainstays in goal-directed medical therapy. Enalapril in particular has been extensively studied and shown to improve survival in HFrEF patients in a number of prospective randomized clinical trials, including CONSENSUS, SOLVD, and V-HeFT II.⁷⁻⁹ The neprilysin inhibitor sacubitril, in combination

with the angiotensin-receptor antagonist valsartan, has been shown to have greater efficacy than enalapril.¹⁰

Endogenous peptides such as brain natriuretic peptide (BNP) have vasodilatory and preload-reducing properties and are released in response to elevated left ventricular pressures, making them attractive targets for heart failure therapy. Neprilysin is a naturally occurring enzyme that degrades BNP. In 2002 omapatrilat, a combination of an ACEI and a neprilysin inhibitor, was compared to enalapril in the OVERTURE trial for treatment of heart failure.¹¹ The primary endpoint was a composite of death and heart failure hospitalization. Omapatrilat was found to be noninferior to enalapril but demonstrated worse outcomes in black patients and higher rates of angioedema compared to the enalapril group. In 2005 nesiritide, a recombinant form of human BNP, in a meta-analysis demonstrated an increased risk of mortality in acutely decompensated heart failure patients compared to the control group.¹² Despite the negative results of these endogenous peptide trials, further attempts to utilize this treatment pathway continued. To reduce the risk of angioedema, a neprilysin inhibitor in combination with an angiotensin receptor blocker (ARB) was studied.

The Angiotensin-Neprilysin Inhibition vs Enalapril in Heart Failure (PARADIGM-HF) trial was the largest prospectively randomized heart failure trial to date.¹⁰ It compared treatment with sacubitril-valsartan to enalapril in patients with HFrEF and NYHA II–IV heart failure symptoms. Patients with symptomatic hypotension, systolic blood pressure <100 mm Hg, hyperkalemia, estimated glomerular filtration rate <30, and previous intolerance to ACEI or ARB were excluded from the trial. The primary endpoint was a composite of cardiovascular death and heart failure hospitalization. All study patients had a run-in period on enalapril, needing to tolerate a dose of 10 mg twice a day for 2 weeks. If patients tolerated therapy, they were randomized 1:1 to continue enalapril or be switched to valsartan-sacubitril.

In PARADIGM-HF, the primary endpoint of cardiovascular death or heart failure hospitalization was seen in 21.8% of patients treated with valsartan-sacubitril and in 26.5% of patients receiving enalapril, with a hazard ratio of 0.80 (confidence interval [CI] 0.73–0.87; $P < 0.001$). Remarkably, both rates of cardiovascular death—13.3% vs 16.5%, hazard ratio of 0.80 (CI 0.71–0.89; $P < 0.001$)—and heart failure hospitalization—12.8% vs 15.6%, hazard ratio 0.79 (CI 0.71–0.89; $P < 0.001$)—were lower in the valsartan-sacubitril group compared to the enalapril group.¹³ The valsartan-sacubitril group had statistically significant higher rates of symptomatic hypotension, while the enalapril group had statistically significant higher rates of cough. Based on the results of the PARADIGM-HF trial, in 2016 the American College of Cardiology/American Heart Association (ACC/AHA) heart failure guidelines were updated to include sacubitril/valsartan for treatment of ACC/AHA stage C HFrEF. The 2016 ACC/AHA/Heart Failure Society of America (HFSA) guidelines recommend starting either

sacubitril/valsartan or an ACEI or an ARB as first-line therapy for ACC/AHA stage C NYHA class II–III HFrEF patients for treatment of angiotensin system inhibition.¹³ The guidelines also recommend replacing an ARB or an ACEI with valsartan-sacubitril to further reduce morbidity and mortality in stage C NYHA class II–III HFrEF patients. Despite having less angioedema than previously studied ACEI/neprilysin, sacubitril/valsartan should not be administered to patients with any history of angioedema. The therapeutic success of valsartan-sacubitril highlights the important role endogenous peptides play in the pathophysiology of heart failure. Research targeting other endogenous vasodilators is ongoing.

EXTRACORPOREAL MEMBRANE OXYGENATION

Extracorporeal membrane oxygenation (ECMO) is a portable modification of cardiopulmonary bypass capable of supporting critically ill patients with refractory cardiopulmonary failure for hours to weeks.¹⁴ Veno-arterial ECMO (VA ECMO) withdraws venous blood via an active pump and returns oxygenated blood into a major central artery. It provides support for cardiac output and has become an important therapy for cardiogenic shock, functioning as a parallel circuit to the patient's heart and lungs.^{15–17}

Accepted indications include shock associated with acute myocardial infarction, myocarditis, intoxication with cardiotoxic drugs, acutely decompensated cardiomyopathies, post cardiectomy, postpartum cardiomyopathy, recurrent life-threatening arrhythmias, and posttransplantation shock when refractory to conventional management.^{14,18,19} VA ECMO has developed a prominent role in management of rapidly progressing heart failure noted as class 1 or 2 of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) or even in patients with cardiac arrest requiring cardiopulmonary resuscitation.²⁰ VA ECMO can be initiated in appropriate candidates if there is evidence of ongoing tissue hypoperfusion and worsening end-organ dysfunction in the presence of escalating inotropic and vasopressor support.¹⁸ Early initiation is important to maximize the potential of cardiac recovery and prevent multiorgan failure.¹⁵ Patients with severe biventricular cardiac failure can be managed with VA ECMO as an alternative to using both right and left ventricular assist devices; each option has its attendant risks.¹⁴

Patients must have a path forward prior to instituting support since this therapy is no more than a bridge to cardiac recovery, heart transplantation, or long-term mechanical circulatory support.^{15,21,22} Compared to other active mechanical circulatory support devices, VA ECMO can be less expensive, allows rapid improvement, and is the only short-term device suitable for severe biventricular failure.^{17,23}

A major disadvantage of this therapy is the lack of ventricular unloading due to creation of elevated afterload, increasing oxygen demand, and wall tension of the myocardium; in addition, blood stasis in the left ventricle will lead to pulmonary edema.^{21,23} Moreover, there are multiple

strategies that could provide left ventricular unloading, like central percutaneous cannulation of the left atrium or ventricle or insertion of an Impella pump (Abiomed, Danvers, MA) inside the left ventricle.^{21,24} Pappalardo et al reported in a retrospective multicenter study in 2016 a statistically significant lower hospital mortality for the VA ECMO plus Impella group compared with the VA ECMO-only group (47% vs 80%, $P < 0.001$); the group received combined support after showing echocardiographic, radiological, and clinical signs of impaired left ventricular unloading or stasis.²¹ Barge-Caballero et al's retrospective series in Spain failed to show any significant clinical benefit of simultaneous intra-aortic balloon pump and VA ECMO for patients in the pre- or post-heart transplant period.²⁵

VA ECMO has become a frequently used method of temporary mechanical circulatory support before heart transplantation and could also be used after surgery in the presence of primary graft dysfunction.^{20,26,27} Implementation of the new United Network for Organ Sharing donor allocation system in the fall of 2018 might result in further growth in use of ECMO in the United States.¹⁶ Overall, patients bridged with VA ECMO to heart transplantation had a higher early posttransplant mortality than patients bridged with durable LVADs as well as nonbridged recipients.²⁸

According to the Extracorporeal Life Support Organization registry, overall in-hospital survival of patients treated with VA ECMO approximates 40%.¹⁵ Acute myocarditis seems to have the most favorable outcomes, with survival to discharge of 55% to 78%,^{16,18,20} with the worst outcomes in patients with congenital heart disease, with survival to discharge of 37%.¹⁶ Regarding VA ECMO therapy for patients with acute cardiac failure, no data from randomized controlled trials are available, as noted in a 2019 Cochrane review on ECMO for critically ill adults.²⁹

Predictors of mortality on VA ECMO include older age, female sex, longer support time, decreased cardiac function at baseline, high lactate concentration, peripheral vascular disease, chronic obstructive lung disease, renal dysfunction, stroke, infection, hypoglycemia, alkalosis, device insertion during cardiopulmonary resuscitation, and decreased urine output¹⁶; therefore, several risk scores have been proposed for assessing the likelihood of survival to hospital discharge, such as the Survival After Veno-arterial ECMO (SAVE) score. This risk score has modest discrimination at best.^{30–32}

The management of patients on ECMO remains complex and resource intensive. As a result, use remains restricted to specialized centers.¹⁶ Currently, not a single blood pump is approved by the US Food and Drug Administration to provide >6 h of circulatory support as ECMO therapy for patients with cardiogenic shock from left ventricular or combined right and left ventricular failure.³³ Despite the latest improvements in mechanical circulatory support devices, therapy of acute refractory heart failure remains challenging, with high mortality rates.²³ In light of the high in-hospital mortality, costs, and ethical issues, appropriate patient

selection for VA ECMO is of paramount importance and requires a multidisciplinary approach and a clear understanding of this therapy and its limitations.^{31,34}

LEFT VENTRICULAR ASSIST DEVICES

In 1961, Domingo Liotta, a gifted Argentinean surgeon, was recruited by Michael E. DeBakey to develop the first artificial heart at the Baylor College of Medicine.^{35,36} The first LVAD emerged from this research³⁷ as the National Heart, Lung, and Blood Institute moved to establish the artificial heart program in 1964. Initial efforts in LVAD development were directed toward mimicking pulsatile flow.³⁸ The Novacor LVAD (World Heart Corp., Oakland, CA) and the pneumatic Heartmate LVAD (Thoratec, Pleasanton, CA) were some of the first pulsatile devices used for short-term support (bridge to heart transplantation) in 1984 and 1992, respectively.^{39,40} The “second-generation” devices (Jarvik-2000, Jarvik Heart, Inc., New York, NY, and HeartMate II, Abbott, Abbott Park, IL) abandoned the pulsatile blood flow paradigm to improve durability.^{41–43} As devices evolved, the INTERMACS registry was established for patients who received durable mechanical circulatory support device therapy in the US in order to study scientific progress, trends, individual program development, and quality assurance.⁴⁴ Intrapericardial devices followed (HeartWare, Medtronic, Fridley, MN), aimed at providing a significant reduction in pump size through smaller centrifugal blood flow pathways. This device also struggled with its own challenges that involved exquisite afterload sensitivity and a higher pump thrombosis rate.^{45–48} The 6-month follow-up data from the Momentum 3 trial were released in 2017.⁴⁵ The data suggested that HeartMate 3 (Abbott, Abbott Park, IL), a centrifugal LVAD, reduced pump thrombosis and strokes. These findings were confirmed in 2019 after data on the full 2-year 1028-patient cohort was released. The device had superior coaxial flow pumps and provided a remarkable improvement in event-free survival, with only a 1% pump thrombosis rate and a 10% stroke rate. (The stroke rate dropped after 6 months of implantation.⁴⁶)

Newer developments in mechanical circulatory support aim to reduce device-related complications and improve survival and quality of life. Innovative surgical techniques involving a lateral thoracotomy and “mini” sternotomy for implantation are already being utilized. Smaller, more ergonomic lithium-ion batteries, Bluetooth connectivity, and new communication systems with easy access to critical data are expected to be available by 2021. Smarter pumps that use software to communicate across device platforms and adjust flows based on patient activity and volume are in the pipeline. Previous attempts to eliminate the driveline using transcutaneous energy transfer systems have been explored in pulsatile LVADs⁴⁷ and the total artificial heart.⁴⁸ In April 2019, two cases of a fully internalized LVAD were reported utilizing a Coplanar Energy Transfer System (Leviticus Cardio, Ltd., Petach Tikva, Israel) to eliminate the driveline

while providing successful energy transmission and up to 8.5 h of unholstered support.⁴⁹ Although promising, such a system is several years away from commercial availability. Today, advanced heart failure patients who are ineligible for cardiac transplantation have alternatives, with durable LVADs providing a notable safety profile, lower health care costs, reduced need for rehospitalizations after discharge, and a survival rate comparable to that of cardiac transplantation at 2 years.^{46,50} Although a durable total artificial heart has yet to emerge, LVAD technology continues to move forward with poise and optimism.

TRANSPLANTATION

On October 18, 2018, the United Network for Organ Sharing put into effect new national listing criteria for candidates awaiting heart transplantation.⁵¹ This change minimized geographic considerations in order to attempt a more equitable distribution of organs. The new allocation system prioritizes the sickest individuals (e.g., those with temporary left ventricular support including VA ECMO) and lowers the priority of individuals on home inotropes or LVADs. This is the natural result of a net neutral impact on total number of transplants.

The new policy creates six statuses to replace the three of the old policy: 1A was changed to status 1, 2, and 3; 1B to status 4 and 5; and 2 to status 6. The new status 1 candidates are defined as individuals on VA ECMO or nondischARGEABLE VADs, while status 2 includes intra-aortic balloon pumps and other percutaneous support devices. Status 3 includes patients on multiple inotropes or a single high-dose inotrope therapy and patients with a dischARGEABLE LVAD with severe but not life-threatening complications. Status 4 includes those who do not fall within the parameters of the previous three statuses, including those on home inotrope therapy, those needing retransplants, those with stable dischARGEABLE LVADs, and those with congenital, ischemic, and infiltrative cardiomyopathies as well as those with amyloidosis and hypertrophic cardiomyopathy.

The intended consequence of removing geographic considerations is that organs will be distributed to the sickest patients first (within 500 miles of the donor). The proportion of transplants within a local zone has decreased by 50%. Whether this is a positive change or not is open to debate. It is unknown how the change will affect long-term posttransplant survival. Ischemic time will increase as teams fly around the country procuring the hearts. The patients being transplanted will be among the sickest on the waiting list; while they will be the most likely to derive benefit from the transplant, they will also be those most likely to experience an adverse outcome. In Texas, the overall number of transplants before and after the new policy has remained unchanged by initial early analysis, but it is still too soon to know how this change will impact any given program.

It is more important than ever for the transplant team to see NYHA functional class III and IV patients earlier rather

than later in order to optimize the timing of their evaluation and their chance of obtaining an organ. Typically, these are individuals with chronic systolic heart failure who have been admitted twice within 6 months for acute decompensation and have an ejection fraction <20% to 25%. Meeting patients earlier will allow time for all the various elements to be evaluated, such as support system, comorbidities, and compliance—none of which can be adequately assessed once the patient is critical in an intensive care unit. Although it remains too early to reach a conclusion regarding the impact of the organ allocation change, waiting times may increase for individuals with end-stage heart failure who are not being supported in the hospital with ECMO or an LVAD.

DISCUSSION

There have been significant advances in the treatment of advanced heart failure over the past 5 years. However, much remains to be done. Future generations will likely look back in astonishment at the “primitive” technology currently in use, especially the need for external components and the dependence on short-lived battery power.

The explosive growth of knowledge currently taking place in medicine challenges physicians to “keep up” and to know when to reach out for specialty assistance and consultation. In advanced heart failure, referrals are often made late, with patients deprived of the benefits of advanced therapies. The 2013 ACC/AHA heart failure guidelines illustrate when providers should consider referring HFrEF patients to advanced heart failure clinicians.¹⁴ In a study highlighting

the importance of early referral, 68,772 HFrEF patients were studied from the National Heart Failure Audit for England and Wales. These patients were discharged from the hospital for heart failure exacerbation from 2007 to 2013 and either did not have follow-up scheduled, followed up with a primary care provider, or followed up with a cardiologist. The researchers found that 30-day mortality (odds ratio 0.7; 95% CI 0.55–0.89) and 1-year mortality (odds ratio 0.81; 95% CI 0.68–0.95) were significantly lower for patients who were referred to a cardiologist after discharge compared to those who were not.⁵²

A reduced ejection fraction <40% should stimulate consideration for referral. Functional limitations with activity and a lack of terminal comorbidities often warrant referral to an advanced heart failure specialist (*Table 1*). Referral made too early is preferred to that made too late.

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Table 1. Guide for referral of patients to advanced heart failure services*	
Criterion	Description
1	Left ventricular ejection fraction <40%
2	Dyspnea at rest or dyspnea, fatigue, or palpitations with ordinary activities of life (New York Heart Association class III to IV)
	Or
	<ul style="list-style-type: none"> Hospitalization for heart failure Implantable defibrillator shocks (if defibrillator present) Arrhythmias (e.g., ventricular tachycardia, atrial fibrillation) Increasing diuretic dosing <ul style="list-style-type: none"> Furosemide ≥160 mg/day Torsemide ≥80 mg/day Bumetanide ≥4 mg/day Worsening renal function <ul style="list-style-type: none"> Creatinine ≥1.6 mg/dL Blood urea nitrogen ≥45 mg/dL Hyponatremia: Sodium <135 mEq/L Unexplained weight loss (cardiac cachexia) Desire for assistance and advice on long-term management
*There is no consensus on exact criteria, and cutoffs for the values cited vary from center to center. This is also true for age. Both 75 and 80 years of age may serve as a threshold for transplantation or advanced mechanical support. We did not include age to encourage individualized assessment and consideration of patients for whom such therapy might be of benefit.	

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Avocations



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