Heart failure (HF) incidence and prevalence is increasing at epidemic proportions. This rise in HF incidence is, in part, due to the success cardiologists have made in salvaging patients who have acute myocardial infarctions. Improved survival in patients with HF and the aging of the population has contributed to the increasing prevalence of HF (1–3). In the United States alone, 5.8 million Americans have HF. The incidence is estimated at 650,000 new cases annually, with over a million annual hospital admissions. More than 300,000 deaths/year are attributed to HF, and the annual cost to manage these patients is close to $40 billion. Approximately 50% of the HF population has heart failure with reduced ejection fraction (HFrEF). In this subset of patients, probably 10% have advanced symptoms (New York Heart Association [NYHA] functional class IIIb to IV), yielding an estimated cohort of approximately 200,000 to 250,000 patients (1–3) who will be the focus of our review.

THERAPEUTIC IMPROVEMENTS IN HFrEF

MEDICAL THERAPIES. Many advances have been made in the management of HFrEF, notably with the use of neurohormonal antagonists. These agents have prolonged survival and improved the quality of life in patients with HFrEF. However, since this therapy was developed in the 1980s and 1990s, newer pharmacological therapies have been few (4). Treatment with the Food and Drug Administration (FDA)-approved selective sinus-node inhibitor ivabradine reduces hospital admission for worsening HF (5). More recently, LCZ696, which combines angiotensin II inhibition with a neprilysin inhibitor, has been demonstrated to hold promise for HFrEF patients (6).

SURGICAL THERAPIES. The greatest advances in HFrEF therapy over the last decade have been surgical approaches (7–9). Biventricular pacing has resulted in improved survival, reverse remodeling, and improved quality of life (10). For patients with refractory HFrEF (i.e., Stage D), progress in cardiac replacement therapies has been substantial. However, palliation with continuous intravenous (IV) inotropes remains the only therapeutic option for many Stage D HFrEF patients, as cardiac replacement therapies with allografts or devices have been offered only to a small subset of these patients. A therapeutic algorithm for Stage D HFrEF is shown in the Central Illustration. In this algorithm, the initial screen is...
elibility for cardiac transplantation, followed by assessment for destination mechanical support, and eventually, palliation. Indeed, in the 2013 International Society of Heart Lung Transplant guidelines for use of mechanical devices, the initial question asked is whether the patient is to be considered a transplant candidate (11). With the rapid advances in mechanical circulatory support, this algorithm may be revised in the near future such that the initial question is eligibility for destination therapy (DT), followed by heart transplantation candidacy and palliation (Central Illustration).

HEART TRANSPLANTATION VERSUS LEFT VENTRICULAR ASSIST DEVICE IN ADVANCED HFrEF

Stage D HFrEF patients are typically referred to cardiac transplant centers, where they undergo an extensive evaluation to determine their candidacy. Optimization of the medical regimen and consideration for revascularization or other standard therapies are assessed. Significant comorbidities that could be life-threatening at the time of transplant surgery or post-transplant are carefully excluded before patients are accepted as transplant candidates (12). The short- and long-term outcomes following cardiac transplantation have been exceptional, with a median survival of 10.7 years and survival conditional on surviving to 1 year after transplant of 13.6 years (13). Quality of life has greatly improved as immunosuppressive agents have become more targeted for the rejection process. This therapeutic success has resulted in a glut of patients awaiting this life-saving therapy.

THE CHRONIC LIMITATION OF ORGAN AVAILABILITY. In the United States, 3,990 patients are currently listed for heart transplant (14-16). The medical urgency of patients listed has steadily increased, with the majority of those now registered for cardiac transplant requiring inotropic or mechanical support. The major limitation to the growth of cardiac transplantation has been the limited donor supply. Despite many campaigns to increase donor volume by local or federal agencies, the donor supply has remained flat and is limited to approximately 2,500 hearts annually in the United States. Currently, warm preservation devices, such as the Organ Care System (Transmedics, Amherst, Massachusetts), which provides a clinical platform for ex vivo human heart perfusion, offer hope for increased numbers of potential donor organs. This device may provide donors beyond the current geographic limit imposed with cold preservation techniques and/or identify viable donors with clinical characteristics that ordinarily would preclude transplant in the absence of a metabolic assessment (17). The recently completed PROCEED II (Randomized Study of Organ Care System Cardiac for Preservation of Donated Hearts for Eventual Transplantation) trial (17) demonstrated noninferiority of ex vivo preservation to cold ischemia in 130 transplant recipients undergoing transplant with standard donors. Three cases of heart transplant using organs from after cardiac death were reported in Australia using this organ preservation system (18). Nevertheless, despite the hope for more usable organs, the donor supply remains flat; clearly transplant is not the solution for the estimated 250,000 patients with advanced HFrEF who could benefit from cardiac replacement therapy. Fortunately, concomitant with the improvement in therapy for heart transplantation, mechanical assist devices to support patients with end-stage HFrEF have continued to evolve. More and more transplant candidates are requiring mechanical support as they wait for an acceptable organ. In 2000, the International Society for Heart Transplantation reported that 19.1% of transplant recipients were mechanically supported; this number increased to 41.0% in 2012 (13). Left ventricular assist device (LVAD) support is typically offered to transplant candidates who are developing end-organ damage despite maximal medical therapy, including inotropic support, or to those candidates who are inotrope-dependent with an anticipated long waitlist time (i.e., large size and/or blood type O recipients). These categories correspond to the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) levels 1 to 3. The INTERMACS is a North American registry established in 2005 that collects clinical data for patients receiving mechanical circulatory support device therapy to treat advanced HF. The INTERMACS scale assigns patients with advanced HF into 7 levels according to hemodynamic profile and functional capacity (Figure 1). Ventricular support devices offer improved survival to transplant with excellent quality of life. However, implantation of the LVAD is another surgical procedure with associated risks, such as stroke, infection, bleeding, and sensitization, that may prolong the time to finding a suitable organ and, in some cases, may preclude transplant.

PATIENT SELECTION FOR HEART TRANSPLANT VERSUS LVAD. In patients with cardiogenic shock or post-cardiotomy syndrome, many short-term mechanical devices provide biventricular support. For chronic patients with Stage D HFrEF who are not transplant candidates, the only mechanical device

ABBREVIATIONS AND ACRONYMS

BTT = bridge to transplant
CF = continuous flow
DT = destination therapy
HF = heart failure
HFrEF = heart failure with reduced ejection fraction
LVAD = left ventricular assist device
MELD = Model for End-Stage Liver Disease
NYHA = New York Heart Association

Figure 1

Figure 1
**CENTRAL ILLUSTRATION** LVAD Versus Transplant: Present and Future for Treating Stage D HF

**CURRENT ALGORITHM**

Does patient meet criteria for heart transplantation?
Exclude patients with significant co-morbidities which could be life threatening at the time of transplant surgery or post transplant

Does the patient meet criteria for destination therapy left ventricular assist device (DT LVAD)?
*Patients with New York Heart Association Class IV symptoms who failed to respond to medical management for ≥45 of the past 60 days, have been intra-aortic balloon pump dependent for 7 days or IV inotrope dependent for 14 days; Left ventricular ejection fraction (LVEF) <25%; Functional limitation with a peak VO₂ <14 ml/min/kg (unless on balloon pump, intravenous inotropes or physically unable to perform exercise test)

**FUTURE PROPOSED ALGORITHM**

Does the patient meet criteria for LVAD as DT Exclude patients with significant co-morbidities which could be life threatening at the time of LVAD implant

Insert approved LVAD; Consider LVAD trials; In select cases, screen for heart transplant; Enroll patient in investigational drug trials; Provide chronic infusion therapy; Recommend hospice

Add patient to heart transplant wait list

In select cases, screen for heart transplant; Enroll patient in investigational drug trials; Provide chronic infusion therapy; Recommend hospice


(Left) Current and (right) future proposed algorithms for treatment of Stage D HFrEF. DT = destination therapy; HFrEF = heart failure with reduced ejection fraction; IV = intravenous; LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; VO₂ = oxygen consumption.

**FIGURE 1** INTERMACS Scale for Classifying Patients With Advanced HF

<table>
<thead>
<tr>
<th>NYHA Class III</th>
<th>Class IIIB</th>
<th>Class IV (Ambulatory)</th>
<th>Class IV (On Inotropes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTERMACS Profiles</td>
<td>7</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Percent of current implants in INTERMACS</td>
<td>1.0%</td>
<td>1.4%</td>
<td>3.0%</td>
</tr>
<tr>
<td>CURRENTLY NOT APPROVED</td>
<td>LIMITED ADOPTION</td>
<td>GROWING ACCEPTANCE</td>
<td></td>
</tr>
</tbody>
</table>


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option is LVAD support. We will focus on the use of long-term LVADs in this patient population.

The criteria for implantation of an LVAD as DT as outlined by the Centers for Medicare and Medicaid Services, are as follows and are derived from the HeartMate I (REMATCH [Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure] [19]) and HeartMate II DT trials [7]:

- Patients with NYHA functional class IV symptoms who have failed to respond to optimal medical management, including angiotensin-converting enzyme inhibitors or beta-blockers, for at least 45 of the past 60 days, or have been intra-aortic balloon pump-dependent for 7 days or IV inotrope-dependent for 14 days;
- Left ventricular ejection fraction <25%; and
- Functional limitation with a peak oxygen consumption <14 ml/kg/min, unless on an intra-aortic balloon pump, IV inotropes, or physically unable to perform the exercise test.

Separation of LVAD patients into bridge to transplant (BTT) and DT populations has been problematic. During their acute illness, many patients may fall into a gray zone with comorbidities that reverse over time. These patients are frequently categorized as “bridge to decision.” In an attempt to normalize end-organ function that currently precludes long-term cardiac replacement therapies, these patients are often supported using extracorporeal membrane oxygenation or short-term single or biventricular assist devices. Selection criteria for DT are less rigid, in some respects, than for transplant candidacy. Table 1 contrasts the key exclusion criteria used in our center for heart transplant and DT candidates.

The presence of certain comorbidities, such as a recent malignancy and elevated pulmonary vascular resistance, may initially disqualify patients from transplant listing, as cancer is more likely to recur during immunosuppression and right HF may occur when the allograft is exposed acutely to severe pulmonary hypertension post-transplant. Patients with significant end-organ dysfunction, such as renal and liver insufficiency, may eventually be reconsidered for transplant if the end-organ function subsequently improves.

Although an elevated pulmonary vascular resistance may not exclude a patient from LVAD implantation, screening for potential right HF is much more rigorous, as no approved chronic right ventricular support is currently available. Patients with severe right ventricular failure may not qualify for LVAD support and, in any case, are likely to require prolonged temporary mechanical right ventricular support and/or inotropes post-operatively. Prediction models, hemodynamic parameters, and echocardiographic measurements are used to assess right ventricular function before LVAD implantation. A prediction score for post-operative right ventricular failure developed by the University of Michigan group incorporates the following variables: use of vasopressors, aspartate aminotransferase, bilirubin, and creatinine levels [20]. Other investigators have focused on hemodynamic parameters, such as right ventricular stroke work index \( \geq 0.25 \text{ mm Hg} \times 1/\text{m}^2 \) [21], the ratio of right atrial pressure to pulmonary capillary wedge pressure \( >0.63 \), and right atrial pressure \( >15 \text{ mm Hg} \) [22]. Other clinicians have emphasized echocardiographic indexes, such as severity of tricuspid regurgitation [23], right to left end-diastolic dimension \( >0.72 \) [24], and right ventricular free-wall strain [25]. However, there are no absolute prediction criteria for the development of intractable right HF while on LVAD support in the short or the long term [11,20–22,26–28].

In contrast, LVAD support is an excellent option for those HFrEF patients with high pulmonary vascular resistance rejected for heart transplant in the setting of adequate right ventricular function [29–31]. Frequently, implantation of the device will allow the vascular resistance to decline and allow these patients to become transplant-eligible [32,33].

Unlike heart transplantation, those HFRST patients with intractable angina or intractable ventricular tachycardia are not device candidates, except in the setting of chronic severe HF symptoms. Due to their small ventricular cavities and frequently normal ejection fractions, patients with restrictive cardiomyopathies are also not LVAD candidates.

| TABLE 1 Center-Specific Differences in Exclusion Criteria for Cardiac Transplant Versus Destination LVADs |
|-------------------------------------------------|-----------------|-----------------|
| Body size | None | BSA <1.2 m$^2$ |
| Age, yrs | >65–72 | None; oldest reported 88 yrs of age |
| PVR, Wood Units | >3 | >8 |
| RV function | None | RVSWI < 250 mm Hg $\times$ ml/m$^2$ |
| Urgent situation | Yes | No |
| Comorbidities | | |
| Malignancy | <5-year disease-free | Chemotherapy non-completed |
| Renal | Creatinine >2.5 mg/dl | Creatinine >3 mg/dl |
| Pulmonary | Mild to moderate | Moderate to severe |
| Obesity | BMI >30 kg/m$^2$ | BMI >45 kg/m$^2$ |
| Intolerance to anticoagulation | No | Yes |
| Restrictive CM | No | Yes |

BMI = body mass index; BSA = body surface area; CM = cardiomyopathy; LVAD = left ventricular assist device; PVR = pulmonary vascular resistance; RV = right ventricle; RVSWI = right ventricular stroke work index.
The need for adequate social support is required for both transplant and mechanical assist device patients, but it is more imperative for device candidates, who may need immediate assistance at home in the event of a serious device alarm.

Age is a key criterion for acceptance for heart transplant that has generated much debate. Some centers will accept candidates in the seventh decade of life, whereas other centers are more conservative (34–36). Results of outcomes of heart transplant in elderly patients have been mixed, whereas outcomes of destination LVADs in this patient population have improved. However, no study has prospectively compared heart transplant with LVAD-DT in elderly patients. Realistically, whether a scarce resource, such as a cardiac allograft, should be used in elderly patients is unclear. With the excellent long-term survival of allografts, the organ can very well outlast the recipient; thus, we may be using a scarce resource for a patient group that may not reap all of its benefits. In reports of alternate list heart transplant candidates, many over 65 years of age who received extended donors, these recipients frequently died, not from cardiac problems, but from comorbidities or the development of new, unforeseen medical problems. The intense immunosuppression needed at the time of transplant can unmask or trigger malignancies. At our center, we performed a retrospective analysis on the use of continuous-flow (CF)-LVADs comparing 23 patients from 65 to 72 years of age with 47 heart transplant recipients in the same age group (36). Those patients selected for LVAD as DT were slightly older and had greater hemodynamic impairment than those who were transplanted. Despite these differences, the 2-year survival rates post-LVAD or -transplant were comparable. Whether the long-term outcomes would be similar is unknown. The choice of the ideal therapy for these patients needs to be studied in a prospective trial.

Statistical survival models that include both BTT and DT LVAD have also been developed. The Model for End Stage Liver Disease (MELD) has been used to prognosticate the risk of patients with cirrhosis undergoing shunt placement and is currently used to risk stratify patients for liver transplant. This formula includes the log transformation of serum creatinine, bilirubin, and prothrombin time international normalized ratio (INR). MELD scores >17 were associated with increased risk for perioperative bleeding and mortality in DT and BTT LVAD patients (37,38). In an analysis of the HeartMate II registry, maintained by Thoratec, Inc. (Pleasanton, California), age, serum albumin, creatinine, INR, and center volume of LVAD surgeries were the strongest parameters in determining 90-day mortality. A HeartMate II Risk Score was derived. Patients were risk stratified by the scores, with a low risk score <1.58 and a high risk score >2.48, using the following equation (0.0274 × [age in years]) − (0.723 × albumin g/dl) + (0.74 × creatinine mg/dl) + (1.136 × INR) + (0.807 × 1 if LVAD volume <15 and 0 if LVAD volume >15) (39). However, subsequent analysis questioned the reproducibility of such scores in discriminating outcomes in high-volume centers (40).

Analysis of the INTERMACS data has provided insights as to characteristics of DT patients who have survival comparable to transplant outcomes. Of the 1,287 DT candidates analyzed from June 2006 to December 2011, of whom 1,160 received CF-LVADs and 128 received pulsatile pumps, 112 patients who were not INTERMACS Level 1, had no prior history of cancer, no previous cardiovascular surgery, and blood urea nitrogen <50 mg/dl comprised the low-risk patients with 1- and 2-year survival of 88% and 80%, respectively. Risk factors for increased mortality included: older age (>75 years), elevated body mass index (>32 kg/m²), history of malignancy, history of cardiac surgery, cardiogenic shock (INTERMACS level 1), dialysis, renal insufficiency (blood urea nitrogen >50 mg/dl), and use of a pulsatile device or a right ventricular assist device (41). Further risk stratification could conceivably be performed to identify subsets of patients who would have survival comparable to transplant, thus helping to decompress the ever-lengthening cardiac transplant recipient waitlist.

With the continued expansion of LVAD therapy as a BTT and DT, cardiac transplantation may eventually become the future bailout strategy for device patients who develop complications. Analysis of United Network of Organ Sharing data already shows a shift in the allocation of organs to more Status 1A patients with device complications (42). The greater numbers of BTT listed as United Network of Organ Sharing 1A due to device malfunction, thrombosis, and infection may negatively affect the current excellent long-term transplant outcomes. In this study, however, infected ventricular assist device patients had significantly lower 1-year post-transplant survival.

LVAD AS DESTINATION

MORTALITY. Most current long-term LVADs have been tested initially as BTT in transplant candidates. Only recently, as devices became more durable, portable, and user-friendly, has this practice pattern begun to evolve toward DT (7–9,19,43–45). Table 2 summarizes the major clinical trials assessing survival on long-term LVADs.
The REMATCH study, published in 2001 (19), was the landmark trial that established the benefit of LVAD therapy in patients with Stage D HFrEF. Although this trial demonstrated a prolongation in survival, the durability and adverse event profile of the pulsatile HeartMate XVE was suboptimal. Subsequent trials using CF-LVADs have demonstrated markedly improved 1-year survival (7–9). Expansion of DT began after the January 2010 approval of the HeartMate II LVAD by the FDA, and since 2012, the number of DT implants has surpassed the number of BTT implants. The number of total LVAD implants for all categories is now greater than the number of annual heart transplant procedures. As reported by INTERMACS, 1-year survival of the 3,931 reported destination LVAD patients from June 2006 to June 2014 was approximately 75%. However, the improvement in technology and medical expertise is also clearly reflected in the superior survival data over the years (Figure 2). The results of HeartMate II post-approval study for DT patients showed 1-year survival of 82% in INTERMACS profiles 4 to 7 (not inotrope-dependent) versus 72% for profiles 1 to 3 (inotrope-dependent). This survival was significantly lower than the 88% 1-year survival for the 2,843 BTT patients, but this is not unexpected given the younger age of the BTT subjects and their fewer significant comorbidities (45,46). Currently, 80% of approved device implants as BTT or DT are for patients in INTERMACS levels 1 to 3 (Figure 1). The ROADMAP (Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients) study is a prospective, multicenter, nonrandomized, observational study that examined the outcome of 200 nontransplant-eligible patients with NYHA functional class IIIb to IV chronic HF not on parenteral inotropic therapy (INTERMACS levels 4 to 7), with a left ventricular ejection fraction ≤25%, and a 6-min walk distance <300 meters (47,48). The results, just presented at the International Society of Heart Lung Transplant 2015 meeting, show a similar mortality of

### TABLE 2 Published LVAD Clinical Trials

<table>
<thead>
<tr>
<th>Study, Year (Ref. #)</th>
<th>n</th>
<th>Device Tested</th>
<th>Indication</th>
<th>Design</th>
<th>Patient Population</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>REMATCH, 2001 (19)</td>
<td>129</td>
<td>HeartMate XVE</td>
<td>DT</td>
<td>Prospective 1:1 HeartMate XVE vs. medical therapy</td>
<td>New York Heart Association functional class IV for 60 days, LVEF &lt;25%, and peak oxygen consumption &lt;14 ml/min/kg (unless on balloon pump, intravenous inotropes, or physically unable to perform exercise test), or intra-aortic balloon pump or IV inotrope dependent for 14 days</td>
<td>1- and 2-yr HeartMate XVE survival of 52% and 23% vs. 25% and 8% on medical therapy</td>
</tr>
<tr>
<td>INTREPID, 2007 (43)</td>
<td>55</td>
<td>Novacor</td>
<td>DT</td>
<td>Prospective nonrandomized</td>
<td>Inotrope-dependent patients</td>
<td>1-yr Novacor survival of 27% vs. 11% on medical therapy</td>
</tr>
<tr>
<td>HeartMate II, 2009 (7)</td>
<td>192</td>
<td>HeartMate II DT</td>
<td>Prospective randomized 2:1 HeartMate II vs. HeartMate XVE</td>
<td>New York Heart Association functional class IIIb or IV symptoms for ≥45 of the last 60 days, LVEF &lt;25%, and peak oxygen consumption &lt;14 ml/min/kg (unless on balloon pump, intravenous inotropes, or physically unable to perform exercise test), or intra-aortic balloon pump dependent for 7 days or IV inotrope dependent for 14 days</td>
<td>1- and 2-yr HeartMate II survival of 68% and 58% vs. 55% and 24% with HeartMate XVE</td>
<td></td>
</tr>
<tr>
<td>HeartMate II post-approval, 2014 (45)</td>
<td>247</td>
<td>HeartMate II DT</td>
<td>Prospective nonrandomized</td>
<td>Consecutive patients eligible for destination DT in INTERMACS</td>
<td>1- and 2-yr survival of 74% and 61%</td>
<td></td>
</tr>
<tr>
<td>HeartMate II, 2007 (8)</td>
<td>133</td>
<td>HeartMate II BTT</td>
<td>Prospective nonrandomized</td>
<td>Transplant candidates</td>
<td>75% survival to transplant, recovery, or ongoing support although remaining eligible for transplant at 6 months</td>
<td></td>
</tr>
<tr>
<td>HeartMate II post-approval, 2011 (44)</td>
<td>169</td>
<td>HeartMate II BTT</td>
<td>Prospective nonrandomized</td>
<td>Consecutive patients eligible for transplant in INTERMACS</td>
<td>90% survival to transplant, recovery, or ongoing support at 6 months</td>
<td></td>
</tr>
<tr>
<td>ADVANCE, 2012 (9)</td>
<td>137</td>
<td>HVAD</td>
<td>BTT</td>
<td>Prospective nonrandomized. HVAD compared with 499 patients who received FDA-approved LVADs in INTERMACS</td>
<td>Transplant candidates</td>
<td>90.7% survival to transplant, recovery, or ongoing support on the original device vs. 90.1% in control group at 6 months</td>
</tr>
</tbody>
</table>

ADVANCE = Evaluation of HeartWare ventricular Assist Device for the Treatment of Advanced Heart Failure; BTT = bridge to transplant; DT = destination therapy; FDA = Food and Drug Administration; HVAD = HeartWare Ventricular Assist Device; INTERMACS = Interagency Registry for Mechanical Assisted Circulatory Support; INTREPID = Investigation of Non Transplant Eligible Patients Who Are Inotrope Dependent; LVAD = left ventricular assist device; REMATCH = Randomized Evaluation of Mechanical Assistance for Treatment of Heart Failure.
~20% in the HeartMate II LVAD and medical arms, but improved functional capacity and quality of life in the LVAD arm at 1 year. However, significant adverse events were much more frequent in the device-supported group versus the medical arm, including bleeding, stroke, ventricular arrhythmias, and rehospitalizations, in addition to problems with pump thrombosis and driveline infections. Of note, 22% of patients in the medical arm transitioned to delayed LVAD placement at 1 year. On the basis of these results, it appears that patients and their physicians may have to weigh the benefit of overall improved functional capacity and quality of life against a real risk of adverse events requiring hospitalizations while on LVAD support, which, in the end, may become inevitable for patients who will fail medical management. Cost-effectiveness of DT may be questioned, with the need for more medical resources on top of the already expensive device implant, hospitalization, and costs for long-term equipment.

ROADMAP is a hypothesis-generating study. REVIVE-IT (Randomized Evaluation of VAD Inter-VENTion before Inotropic Therapy) was a National Heart, Lung, and Blood Institute (NHLBI)-sponsored prospective, randomized trial for the evaluation of HeartMate II LVAD as DT intervention in NYHA functional class III chronic HF before inotropic therapy (49). However, the data and safety monitoring board recommended that the National Heart, Lung, and Blood Institute closed the study due to lack of clinical equipoise.

MORBIDITY. Despite the improved survival, there continue to be frequent long-term complications associated with CF-LVADs. The post-approval HeartMate II DT study reported a high probability of device-related adverse events in patients at 2-year follow-up: driveline infections (19%), sepsis (19%), strokes (11.7%), thrombus formation (3.6%), bleeding (54%), mechanical failures requiring replacement (4%), and right HF (18%) (45). In addition, acquired von Willebrand’s disease rapidly develops in virtually all patients post-CF-LVAD implant (50). Aortic insufficiency is also frequent, with an incidence of >30% at 3 years (51). A report of an increased rate of pump thrombosis since 2011 has been published (52). The etiology for this observation is unclear, and it is likely a multifactorial process that might have resulted from less frequent use of perioperative heparin, lower target INR ranges due to the high incidence of bleeding, inadequate antiplatelet therapy, overestimation of effective anticoagulation by the partial prothrombin time, abnormal angulation of inflow or outflow cannulas, infections, use of erythropoietic factors, and/or other factors not yet identified (50,52-55).

The event rate in device-supported patients resulting in rehospitalization for infection, bleeding, device malfunction, stroke, or death is extremely high, at 70% in the first year (46). The recent ROADMAP study confirmed a high incidence of adverse events even in “less sick” patients (see earlier discussion) (48). Thus, ongoing research is needed to develop newer and improved devices.

EVOLUTION OF LVAD TECHNOLOGY

PAST AND PRESENT. The rapid evolution of mechanical circulatory support for the treatment of advanced HFrEF has been remarkable. In 1969, the first total artificial heart was implanted. However, several issues hampered the expansion of total artificial heart technology. Limited durability, an excessive rate of complications, the risk of sudden device interruption and death, and elimination of the possibility of native cardiac recovery limited its use to severe biventricular failure (i.e., CardioWest, SynCardia, Tucson, Arizona) and shifted the focus to the development of LVAD technology (Figure 3). First-generation volume displacement LVADs used a diaphragm and unidirectional valves to replicate the pulsatile cardiac cycle through diastolic filling and systolic emptying of the
device. The results of the REMATCH trial (19) led to FDA approval of the HeartMate XVE for DT in 2002. However, despite these results, first-generation pulsatile pumps were not widely used, with only 119 DT implants in 2003, rising to 377 in 2005. Physicians and patients had concerns regarding the large pump size, adverse events, and limited durability, with uniform failure after 18 to 30 months of support. HeartMate XVE production has been discontinued.

Over the past 2 decades, CF-LVAD technology has quickly developed, primarily due to its durability and the miniaturization of pump size. Contemporary second- and third-generation LVADs are valveless pumps that utilize a permanent magnetic field designed to rapidly spin a single impeller supported by mechanical or, more recently, hydrodynamic or magnetic bearings (Table 3). Second-generation axial pumps have the impeller outflow directed parallel to the axis of rotation. The rotor spins on mechanical (HeartMate II, Jarvik 2000 [Jarvik Heart, New York, New York], and HeartAssist 5 [ReliantHeart, Houston, Texas]) or contact-free bearings (Incor, Berlin Heart, Berlin, Germany). Third-generation centrifugal pumps have the impeller outflow directed perpendicular from the axis of rotation (HeartWare Ventricular Assist Device [HVAD] [HeartWare, Framingham, Massachusetts] and HeartMate III). Other pumps use a mixed design, where blood flow follows the axis of rotation but exits...
<table>
<thead>
<tr>
<th>Device</th>
<th>Manufacturer</th>
<th>Design</th>
<th>Bearings</th>
<th>Position</th>
<th>Weight (g)</th>
<th>Maximal Flow (l/min)</th>
<th>Special Features</th>
<th>Trials</th>
<th>FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>HeartMate II</td>
<td>Thoratec</td>
<td>Axial</td>
<td>Mechanical</td>
<td>Pre-peritoneal or intra-abdominal</td>
<td>281</td>
<td>10</td>
<td>&gt;10 yrs of experience</td>
<td>BTT and DT trials completed in the United States, results published (8,19,44,45)</td>
<td>BTT 2008; DT 2010</td>
</tr>
<tr>
<td>Jarvik 2000</td>
<td>Jarvik Heart</td>
<td>Axial</td>
<td>Mechanical</td>
<td>Pericardial</td>
<td>90</td>
<td>7</td>
<td>Minimally-invasive option with outflow graft to descending aorta; post-auricular driveline (-infection); low-speed operation (8 s/min) allowing aortic valve opening</td>
<td>Commercially available in Europe; BTT completed in the United States, results not published; DT ongoing in the United States</td>
<td>Investigational</td>
</tr>
<tr>
<td>Incor</td>
<td>Berlin Heart</td>
<td>Axial</td>
<td>Hydrodynamic</td>
<td>Pericardial</td>
<td>200</td>
<td>8</td>
<td></td>
<td>Commercially available in Europe; no ongoing trials in the United States</td>
<td>Investigational</td>
</tr>
<tr>
<td>HeartAssist 5</td>
<td>ReliantHeart</td>
<td>Axial</td>
<td>Mechanical</td>
<td>Pericardial</td>
<td>92</td>
<td>10</td>
<td>Direct flow measurement; remote monitoring and device interrogation akin to pacemakers and defibrillators</td>
<td>Commercially available in Europe; BTT trial in the United States expected to start in 2015</td>
<td>Investigational</td>
</tr>
<tr>
<td>HVAD</td>
<td>HeartWare</td>
<td>Centrifugal</td>
<td>Hydrodynamic</td>
<td>Pericardial</td>
<td>145</td>
<td>10</td>
<td>&gt;5 yrs experience</td>
<td>BTT trial completed in the United States, results published (9); DT trial completed; supplemental cohort ongoing in the United States</td>
<td>BTT 2012</td>
</tr>
<tr>
<td>HeartMate III</td>
<td>Thoratec</td>
<td>Centrifugal</td>
<td>Magnetic</td>
<td>Pericardial</td>
<td>200</td>
<td>10</td>
<td>Pump speed modulation; antithrombotic cycling (washout) and &gt;pulsatility</td>
<td>Feasibility trial ongoing in the United States</td>
<td>Investigational</td>
</tr>
<tr>
<td>MVAD</td>
<td>HeartWare</td>
<td>Mixed</td>
<td>Hydrodynamic</td>
<td>Pericardial</td>
<td>92</td>
<td>6.5</td>
<td>Pump speed modulation; antithrombotic cycling (washout) and &gt;pulsatility. Potential biventricular support</td>
<td>Feasibility trial expected to start in Europe in 2015</td>
<td>Investigational</td>
</tr>
</tbody>
</table>

HVAD = HeartWare Ventricular Assist Device; MVAD = miniature ventricular assist device; other abbreviations as in Table 2.
perpendicular to the inflow (miniature ventricular assist device [MVAD] [HeartWare]). The design of most recent pumps is contact-free, with no mechanical bearings and an impeller suspended using magnetic and/or hydrodynamic systems. One consideration in avoiding mechanical bearings is that formation of a small thrombus on the metal could lead to overheating and propagation of the thrombus. Hydrodynamic levitation, in contact-free systems, uses a layer of blood (blood bearing) to lift the rotor (Incor, HVAD, and MVAD). Full magnetic levitation utilizes magnetic bearings only to levitate the rotor (HeartMate III). Avoiding hydrodynamic bearings may reduce the risk that small pieces of foreign matter, such as a thrombus, disrupt the operation of the rotor, leading to additional thrombus formation and pump dysfunction.

In CF-LVADs, pump blood flow is directly proportional to rotor speed and inversely proportional to the pressure differential between the left ventricle and aorta. However, axial and centrifugal pumps differ in their hydrodynamic performance, as characterized by the relation between flow rate and head pressure (the pressure gradient across the pump, i.e., the differential pressure between the inlet in the left ventricle and the outlet in the aorta) (Figure 4) (56,57). Axial flow pumps show a steep and inverse linear relationship between flow and head pressure. In contrast, this relationship is flatter and more susceptible to head pressure changes (i.e., more sensitive to pre-load and afterload) in centrifugal pumps. With the same change in pressure, centrifugal pumps generate larger changes in flow, ranging from 0 to 10 l/min, whereas the axial flow pump flow ranges from 3 to 7 l/min (Figure 4). These hydrodynamic characteristics of centrifugal pumps translate into: 1) a more pulsatile waveform; 2) a more accurate flow estimation; and 3) a lower risk of suction events (e.g., in a setting of dehydration, arrhythmias, or right ventricular failure); but also 4) more dependency of device flow on loading conditions when compared with axial flow pumps (56–58).

**FUTURE DIRECTIONS.** Pulsatility, further miniaturization, total implantability and remote monitoring dominate current trends in the evolving technology of present-day LVADs.

**Pulsatility.** Complications related to aortic valve insufficiency, gastrointestinal bleeding, pump thrombosis, and stroke have hampered long-term results and thereby limited the expansion of LVAD technology. Low arterial pulsatility has been implicated in the development of several serious adverse effects of CF-LVADs. For example, persistently diminished pulsatility may contribute to the development of arteriovenous malformations (58), and continuous left ventricle unloading decreases the frequency of aortic valve opening, promoting commissural fusion and, ultimately, aortic insufficiency (51,59). Additionally, a closed aortic valve predisposes to stasis and clot formation above the closed valve. Thus, recent research...

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**FIGURE 4** Relationship Between Head Pressure and LVAD Flow in Axial and Centrifugal Pumps and the Effect on Pulsatility

![Diagram showing relationship between head pressure and LVAD flow in axial and centrifugal pumps.](http://content.onlinejacc.org/)  

Modified with permission from Pagani (56). AoP = mean aortic pressure; LPM = liters per minute; LV = left ventricle; LVAD = left ventricular assist device; LVP = left ventricular pressure; P = pressure; Q = flow.
has focused on methods to generate more pulsatility and (intermittent) aortic valve opening. This can be achieved using pump speed modulation (i.e., intermittent lower-speed pump operation) that: 1) generates intrinsic pulsatile flow from the LVAD itself; and/or 2) allows the native left ventricle to periodically create pulsatile flow during conditions of increased ventricular loading (Jarvik 2000, HeartMate III, and MVAD).

Pump speed modulation can be independent of the native heart rate (asynchronous) or consistent with native heart rate (synchronous). Synchronous

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**FIGURE 5 Hemodynamic Curves Without and With HVAD Support**

Sample hemodynamic waveforms recorded in a chronic ischemic HF bovine model without pump support (HF baseline) and with the HVAD at constant speed, copulse, counterpulse, and asynchronous modulation. Modified with permission from Soucy et al. (61). HVAD = HeartWare Ventricular Assist Device; IHF = ischemic heart failure; LVADF = left ventricular assist device flow; other abbreviations as in Figures 1 and 4.
modulation can be programmed to deliver maximum LVAD flow during left ventricle systole (copulsation) or during diastole (counterpulsation) (60,61). Counterpulsation maximizes left ventricle unloading, thereby providing the best resting conditions for the failing heart. Copulsation enhances pulse pressure but decreases the likelihood of aortic valve opening, because LVAD flow, and thereby arterial pressure, increases during cardiac systole (62). Asynchronous mode offers the advantage of not requiring a triggering source and theoretically combines the physiological benefits of intermittent copulse-counterpulse support (Figure 5) (61).

Additionally, LVAD speed modulation can be used for antithrombotic cycling to prevent pump thrombosis, one of the most feared and life-threatening complications, by precluding the formation of zones of recirculation and stasis within the device (i.e., washout). In the future, speed modulation algorithms might respond to specific physiological demands, such as those related to exercise or states of extreme hypertension or hypotension, arrhythmias, baroreceptor signaling and/or hormonal changes (63).

**Miniaturization.** Smaller devices offer several potential advantages such as: 1) minimally-invasive surgery via a left thoracotomy without cardiopulmonary bypass; 2) fewer size and sex limitations; and 3) potential for both left and right ventricular long-term support, the latter of which has already been described in several cases using HVADs (64), thus preventing the need for a totally artificial heart in severe biventricular failure.

**Total implantability.** A fully-implantable system that is rechargeable transcutanously is an option desired by patients. However, several technical challenges remain. Two large discontinued pulsatile systems, the AbioCor total artificial heart and the LionHeart LVAD, used transcutaneous energy transfer systems to transmit power across the skin. Theoretical advantages include: 1) the absence of driveline exit site, which would eliminate driveline infections; 2) improved patient acceptance of LVAD therapy: no driveline, ability to remove all externally worn equipment for a period of time; 3) participation in activities such as bathing and swimming, where the body is completely submerged in water. Potential disadvantages include: 1) risk of internal infection of implanted material; 2) component failure or migration requiring elective (similar to a pacemaker or a defibrillator generator change) or emergent surgical intervention; 3) bleeding risk and pain from all implanted components; 4) size and sex limitation due to the large cumulative volume of all implanted parts.

Time is needed to address these challenges and to optimize a fully-implantable system before human studies can resume.

**Remote monitoring.** Akin to the advances seen in defibrillator and pacemaker therapy, remote device monitoring is another future goal of LVAD technology. The HeartAssist 5, which is currently being tested in Europe, carries a “cell phone system” within the controller that transmits flow, power, and speed data every 15 min. These LVAD parameters as well as alarm notifications can be promptly delivered to health care providers via text messages or e-mail.

**LVAD therapy and recovery**

Mechanical support results in profound volume unloading in the left ventricle. This causes dramatic reductions in ventricular size and shape, followed by structural, biochemical, and genetic changes, leading to a phenomenon called reverse remodeling. There is a marked shift in the left ventricle end-diastolic pressure-volume relationship toward normal. Some clinical reports have described a high rate of myocardial recovery when coupled with high-dose neurohormonal blockade and β-2 agonist therapy with clenbuterol (65,66). Most studies in the United States have not been able to reproduce these findings and observe recovery rates <10%, although one recent prospective trial at a single U.S. center reported a 19% recovery rate with full neurohormonal blockade (43,67–74). Yet, the potential for LVADs to be used as a tool to rest the heart and, in these settings, to test newer therapies that can reverse myocardial dysfunction is very intriguing. A recent clinical trial using intramyocardial injections of mesenchymal stem cells at the time of LVAD surgery reported a trend toward improved tolerability of weaning from mechanical support (75).

**Conclusions**

LVADs represent a significant advancement in the field of advanced HF. Device technology continues to evolve rapidly. Patient survival is improving, despite the many device-related complications. Future clinical trials are needed to determine who would benefit most from device support versus cardiac transplantation and whether LVAD support may favor cardiac recovery.

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**KEY WORDS** heart assist devices, heart failure, heart transplantation