MAYO CLINIC

REVIEW

Current Status of Left Ventricular Assist Device Therapy

Pavol Sajgalik, MD; Avishay Grupper, MD; Brook S. Edwards, MD; Sudhir S. Kushwaha, MD; John M. Stulak, MD; David L. Joyce, MD; Lyle D. Joyce, MD, PhD; Richard C. Daly, MD; Tomas Kara, MD, PhD; and John A. Schirger, MD

Abstract

Congestive heart failure (HF) remains a serious burden in the Western World. Despite advances in pharmacotherapy and resynchronization, many patients have progression to end-stage HF. These patients may be candidates for heart transplant or left ventricular assist device (LVAD) therapy. Heart transplants are limited by organ shortages and in some cases by patient comorbidities; therefore, LVAD therapy is emerging as a strategy of bridge to transplant or as a destination therapy in patients ineligible for transplant. Patients initially ineligible for a transplant may, in certain cases, become eligible for transplant after physiologic improvement with LVAD therapy, and a small number of patients with an LVAD may have sufficient recovery of myocardial function to allow device explantation. This clinically oriented review will describe (1) the most frequently used pump types and aspects of the continuous-flow physiology and (2) the clinical indications for and the shift toward the use of LVADs in less sick patients with HF. Additionally, we review complications of LVAD therapy and project future directions in this field. We referred to the Interagency Registry for Mechanically Assisted Circulatory Support, landmark trials, and results from recently published studies as major sources in obtaining recent outcomes, and we searched for related published literature via PubMed. This review focuses primarily on clinical practice for primary care physicians and non-HF cardiologists in the United States.

 ■ Mayo Clin Proc. 2016;91(7):927-940

Heart failure (HF) remains a major burden in terms of both morbidity and mortality in the United States and the Western World.[1,2] Although advances in pharmacological[3-5] and resynchronization device[6] therapy have led to reverse myocardial remodeling with symptomatic and survival benefit, many patients with HF have progression to end-stage disease. These patients have a poor quality of life with recurrent hospitalizations and a high mortality rate.[7] Therapeutic options for these patients include cardiac transplant or left ventricular assist device (LVAD) therapy. Although it remains the gold standard treatment for this population, cardiac transplant is limited by organ availability, fixed pulmonary vascular resistance due to prolonged advanced HF status, and other comorbidities in potential recipients.[8] In 2001, the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial found that LVAD therapy is superior to medical therapy in end-stage HF, with a 48% reduction in death from all causes.[9] Nevertheless, the most significant improvement was due to new technology with continuous-flow (CF) pumps.[10,11]

For patients with advanced HF, implantation of an LVAD has emerged as a bridge to transplant (BTT) or as destination therapy (DT) for those who are ineligible for transplant.[10,12] Left ventricular assist devices can be a bridge to decision for patients who are ineligible for transplant at the time of LVAD implantation but may become eligible after the procedure[13] and may also be utilized to promote myocardial recovery in a bridge to recovery strategy. Clinical trials have revealed the ability of the CF-LVAD to provide adequate support in both the BTT and DT settings,[14-18] and indeed, patients are reported to have been supported by the HeartMate (HM) II

From the Division of Cardiovascular Diseases (P.S., A.G., B.S.E., S.S.K., T.K., J.A.S.) and Division of Cardiovascular Surgery (J.M.S., D.L.J., L.D.J., R.C.D.), Mayo Clinic, Rochester, MN; and Department of Internal Medicine, Cardioangiology, International Clinical Research Center, St. Anne's University Hospital, Brno, Czech Republic (P.S., T.K.).

ARTICLE HIGHLIGHTS

- Left ventricular assist device (LVAD) therapy has become an accepted intervention for the treatment of late-stage heart failure because of the lack of organ donors.
- This review presents up-to-date information regarding indications, outcomes, complications, and future directions in the field of LVAD therapy.
- Left ventricular assist device therapy is commonly used as a bridge to heart transplant; however, the use of LVADs as a destination therapy is increasing, now providing long-term cardiac support.
- Early recognition of potential LVAD candidates and optimal timing of implantation improves clinical outcomes of LVAD therapy.
- A multidisciplinary approach is required to minimize complications of LVAD therapy.
- Future research should focus on the potential of LVAD therapy to promote cardiac recovery in selected populations.

(Thoratec Corporation), a CF-LVAD, for more than 5 years.[17] Excellent comprehensive guides for the management of patients with LVADs have been published previously.[19,20] This article reviews the use of LVAD therapy in these settings and explores future directions in this field.

LVAD PUMP TYPES: FROM PULSATILE- TO CONTINUOUS-FLOW DEVICES AND BACK TO ARTIFICIAL PULSATILITY

The LVAD systems consist of an inflow cannula placed in the apex of the heart, the pump itself, and an outflow conduit sutured to the aorta. A driveline is tunneled from the pump out of the body through an exit site to a belt controller and batteries. The HM II (Figure 1),[21] the successor to the pulsatile-flow (PF) HM XVE, provides CF via an axial propeller. The absence of a reservoir chamber and 1-way valves makes the device considerably smaller than the XVE,[22,23] allowing for use in a wider range of patients, including small adults and children.[14,23]

Other CF pumps utilize a magnetically levitating rotor system or hydrodynamic bearings to decrease mechanical wear, theoretically reducing hemolysis and the incidence of pump thrombosis. This group includes the HeartWare (HeartWare Inc) device (Figure 2),[24] a miniaturized centrifugal pump with a short inflow cannula that enables intrapericardial placement without pump pockets and abdominal operations that potentially can also be considered for right ventricular (RV) failure support as an off-label use. Studies have demonstrated successful utilization of this pump as a BTT strategy.[24-29]

Although a clear survival advantage with reliable CF pumps has been documented,[21] speculation has been raised regarding the physiologic impact of PF vs CF. Continuous-flow ventricular output negatively impacts nitric oxide production,[30] inflammatory biomarkers (ie, tumor necrosis factor α, C-reactive protein),[31] endothelial function,[31-33] and, in turn, organ microcirculation.[34,35] Animal models have revealed impaired gas exchange during CF.[36] The CF results in up-regulation of the renin-angiotensin system, and glomerular periarteritis has been noted with CF.[37] Newer generation pumps like, the HM 3 (Thoratec Corporation), a magnetically levitated CF-LVAD with artificial pulsatility, is being evaluated prospectively in the MOMENTUM 3 US IDE Clinical Trial for DT and BTT indications.[38] Thirty-day mortality was 2%, and 6-month survival was 92%, which exceeded the 88% performance goal.[29]

INDICATIONS, RISK FACTORS, AND EXCLUSION CRITERIA FOR LVAD THERAPY

Advanced HF is clinically defined as severe circulatory compromise requiring special care, including heart transplant (HTx), continuous inotropic therapy, mechanical cardiac support (MCS), or hospice care.[39] Patients who have refractory advanced HF symptoms despite optimal medical therapy may be considered for LVAD therapy, either as DT or as BTT. Patients listed for HTx are potential candidates for an LVAD as BTT. The placement of an LVAD may be required in those with severe symptomatic HF despite optimal medical therapy, especially if the patient's body size and blood type indicate that the wait for a possible donor organ will be prolonged. The large clinical trials for LVAD therapy include patients with New York Heart Association (NYHA) class IV symptoms, ie, substantially decreased exercise capacity due to cardiac limitation. The

Mayo Clin Proc. ■ July 2016;91(7):927-940 ■ http://dx.doi.org/10.1016/j.mayocp.2016.05.002
www.mayoclinicproceedings.org

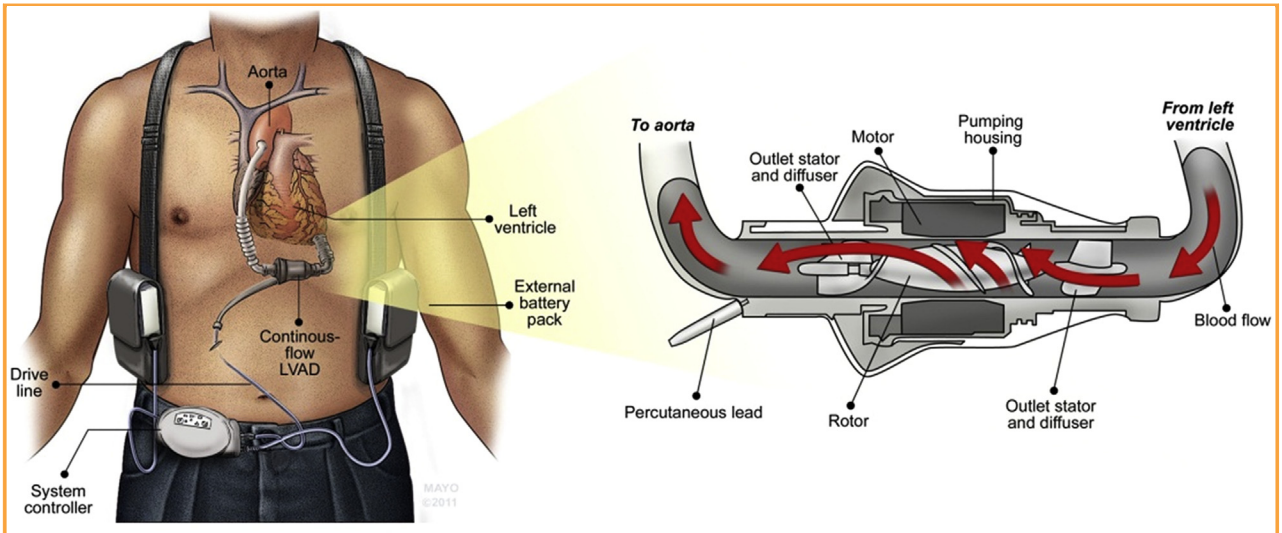

FIGURE 1. HeartMate II device system. From *N Engl J Med*, used by permission of Mayo Foundation for Medical Education and Research. All rights reserved.[21]

threshold for peak oxygen consumption of less than 14 mL/kg per minute (or <50% of expected volume) and a reduced 6-minute walk distance of less than 300 m[40] are not explicitly required for BTT indication, but these parameters are considered in transplant evaluation. Similarly, current recommendations for the use of MCS do not include the hemodynamic criteria needed for BTT (ie, decreased ejection fraction of <25% or a cardiac index of <2.2 L/min per m^2).[40] Progressive cardiac cachexia and renal and hepatic dysfunction due to poor perfusion, pulmonary venous hypertension not responding to conventional treatment, systemic hypotension, and unmanageable angina not responsive to therapy or revascularization may suggest the need for LVAD support as a BTT strategy.[41,42] In specific circumstances, refractory ventricular tachycardia/fibrillation may be treated with LVAD implantation[43] during failed catheter ablations or when multiple implantable cardioverter-defibrillator shocks may further worsen ventricular function[44] and may cause severe psychological distress.[45] Data from our institution indicate that patients with end-stage HF caused by restrictive and hypertrophic cardiomyopathy may benefit from LVAD therapy and have 1-year survival comparable to that of those with ischemic or dilated cardiomyopathy treated with LVAD therapy.[46] Most patients with complex congenital heart disease are not candidates for MCS, although careful preoperative consideration may permit successful implantation in highly selected cases.[47] Unrecognized patent foramen ovale or atrial septal defects can contribute to hypoxemia from right-to-left shunting after LVAD implantation and paradoxical emboli. An investigation for the implantation of a shunt should be performed preoperatively or intraoperatively, and repair should be performed during LVAD implantation.[40]

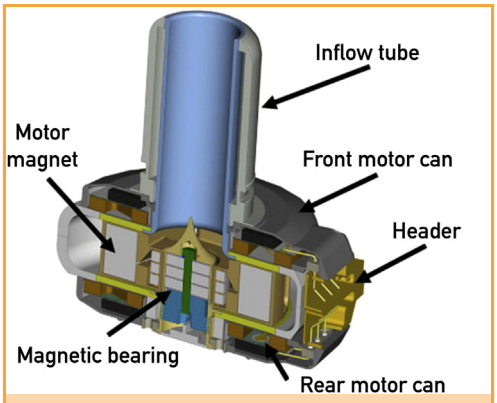

FIGURE 2. Cross-section view of the HeartWare pump. LVAD = left ventricular assist device. From From *J Heart Lung Transplant*, with permission.[21]

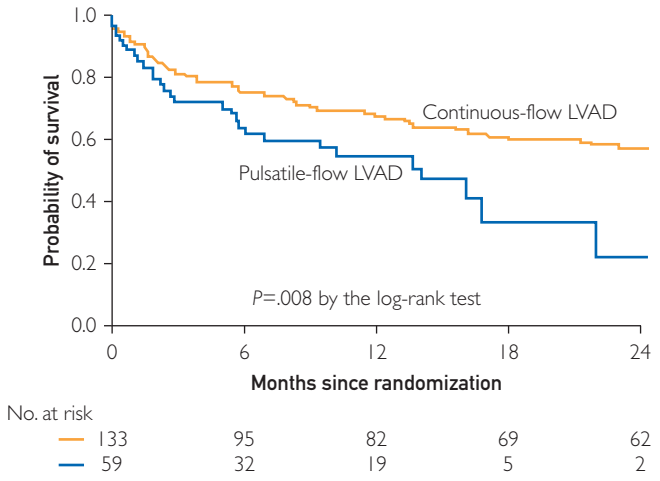

FIGURE 3. Kaplan-Meier estimates of survival from the as-treated analysis, according to treatment group. The data shown are for the 192 patients who received a left ventricular assist device (LVAD). Of the 59 patients who had a pulsatile-flow LVAD, 20 had the device replaced during the study period, with 18 (31%) receiving a continuous-flow LVAD instead of another pulsatile-flow LVAD. By 2 years, only 2 patients had a pulsatile-flow LVAD, both of whom had replacement devices. From *N Engl J Med*, used by permission of Mayo Foundation for Medical Education and Research. All rights reserved.[21]

Because the optimization of HF therapy and on-time LVAD implantation can minimize irreversible end-organ changes that negatively affect survival,[18] the role of primary care physicians and non-HF cardiologists lies in the early recognition of HF symptoms and referral of patients to an HF specialist. The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles identified patients at risk for complications after MCS. This valid score system should be considered as a tool to assess a patient's profile to predict complications and mortality after MCS implantation. Current INTERMACS data support LVAD implantation in earlier functional levels.[40,44,48,49] This finding raises the importance of timely referral by primary care physicians and non-HF cardiologists. Although each case is judged individually, the traditional Lietz-Miller risk score, weighted from hemodynamic, hematologic, and metabolic components, can be utilized to estimate 90-day mortality.[50]

Exclusion criteria for BTT patients are the same as for cardiac transplant candidates.[41,42] Patients initially excluded from transplant may receive an LVAD as either DT or as a bridge to decision. Such cases include younger patients who have been treated for cancer and may require time before transplant[4,37] or patients with severe pulmonary hypertension that could reverse after unloading the left ventricle with an LVAD.[26,27]

After the success of BTT in ambulatory patients with remarkable improvement in functional status and quality of life,[35] the use of MCS for DT was investigated. The landmark trial of DT, REMATCH confirmed superior survival rates for patients supported by the HM XVE vs optimal medical treatment. The 48% risk reduction in mortality led to US Food and Drug Administration (FDA) approval of this pulsatile device for DT in 2002.[9] Subsequently, the CF pump HM II was approved by the FDA for DT in 2010 on the basis of a multicenter, randomized study that compared the HM XVE and HM II on the basis of almost 200 transplant-ineligible patients with a 2-year survival of 58% (HM II) vs 24% (HM XVE) (Figure 3).[21]

Destination therapy serves patients who are ineligible for HTx primarily because of age, and in recent years, it increasingly substitutes for HTx because of the lack of organ donors.[51] Predicted mortality at 2 years without receiving LVAD therapy should exceed the predicted mortality at 2 years with LVAD therapy. Age does increase the risk for complications during and after LVAD implantation.[52] Our group has successfully placed, and utilized, LVADs in patients more than 80 years old; nevertheless, caution is indicated in these settings, and some geriatric scores such as fragility indices[53] can be used for the stratification of elderly candidates. Further parameters indicating caution in LVAD implantation for DT include active cancers with a life expectancy less than the expected survival with an LVAD; recent intracerebral bleeding; active systemic infection and/or bacteremia and septicemia; and coagulopathy. Direct thrombin inhibitors have been used successfully in the postoperative management of patients with heparin-induced thrombocytopenia.[41] Because of higher bleeding risk, extreme caution is recommended when using direct thrombin inhibitors at the time of operation; an alternative is the utilization of plasmapheresis to lower heparin-associated antibody titers before and during operation.[54] However, a 4-fold increased risk of reoperation for

Mayo Clin Proc. ■ July 2016;91(7):927-940 ■ http://dx.doi.org/10.1016/j.mayocp.2016.05.002
www.mayoclinicproceedings.org

bleeding over standard open heart surgical procedures remains.[55] Often, poor nutrition, hepatic congestion with abnormal coagulation, and high venous pressures contribute to surgical bleeding risk, which is amplified by increased age.[55] Poor wound healing, increased risk of infection, and higher risk for postoperative death is associated with cardiac cachexia with albumin levels of less than 3.5 g/dL (to convert to g/L, multiply by 10) and total protein concentrations of less than 6 g/dL (to convert to g/L, multiply by 10). Nutritional issues must be addressed before implantation to optimize outcomes.[56] Although obesity increases the risk of driveline infection,[57] 1-year survival of morbidly obese patients with HF who received an LVAD as DT was not different from 1-year survival of patients with normal weight.[58]

Furthermore, patients with an LVAD could lose weight or undergo weight management to become acceptable candidates for transplant. Increasing interest in including bariatric operation before or after LVAD implantation may reduce potential complications.[59] Active infection is a contraindication to LVAD implantation. Aggressive treatment and close collaboration with infectious disease specialists is required for optimal timing of implantation because it is difficult to sterilize a seeded device with antibiotics.[60] Currently, because the HeartWare LVAD is implanted intrapericardially, body size is not limiting. This remarkable shift in pump size from robust pulsatile devices allows implantation of the pump in adolescents, smaller adults, and a significantly higher percentage of women.[60] The exclusion criteria for DT are less well defined. Relevant surgical contraindications to LVAD placement include a history of multiple previous sternotomies with extensive subsequent scaring and fibrosis. In the past, aortic regurgitation was considered a contraindication to LVAD placement; however, the aortic valve can be closed if necessary by placing a coaptation stitch at the central portion of the cusps to ensure aortic valve competence.[61,62] Of note, tricuspid valve repair or replacement can also be undertaken in the setting of severe tricuspid regurgitation at the time of LVAD placement.[63] Psychosocial evaluation is an integral part of the preimplant evaluation. Chemical dependencies, previous nonadherence, lack of an adequate support system, underlying mental illness, and intellectual disability could affect postoperative outcomes and should be addressed by a psychiatrist and social worker.

The decision to proceed with LVAD implantation may be informed in respect to the projected trajectory of life. Numerous clinical scoring systems have been developed, but no single parameter is a perfect predictor of HF prognosis. The Heart Failure Survival Score, employed in the selection of patients for cardiac transplant, and the Seattle Heart Failure Model score, accessible as a Web-based tool,[64] are commonly used in this setting.[65,66] Neither the Seattle Heart Failure Model score nor the Heart Failure Survival Score acknowledges the effect of other illnesses. However, comorbidities are incorporated in the scoring system used in the EFFECT (Enhanced Feedback for Effective Cardiac Treatment) study[67] and in the prognostic estimation of the CardioVascular Medicine Heart Failure index.[68] These complex scoring systems are not required for prognostication in most elderly patients with advanced HF. Clinically, progressive cardiac cachexia, renal dysfunction, and escalating diuretic dose requirements usually provide sufficient evidence of an irreversible and ever-declining health status.[69,70] Recurrent episodes of decompensation within 6 months despite optimal tolerated therapy, the occurrence of malignant arrhythmias, the need for frequent or continual intravenous therapies, long-term poor quality of life, and intractable NYHA class IV symptoms are usual triggers for palliative care discussion.[71] At the Mayo Clinic Transplant Center in Rochester, Minnesota, we closely cooperate with the palliative care group for the optimization of treatment and management of patients' symptoms, including close discussions with family. Strategies for improving communication and enhancing patient-centered decisions are actively explored in the ongoing Decision Support Intervention for Patients and Caregivers Offered Destination Therapy Heart Assist Device (DECIDE-LVAD) trial.[24]

SHIFT TO PATIENTS WITH LESS ADVANCED HF

The number of LVAD implantations has grown rapidly in recent years.[49] The very

good outcomes in patients receiving LVADs who have relatively hemodynamically stable conditions,[14,20,24] often electively admitted for the surgical procedure, have led to investigating outcomes with the use of LVADs vs standard medical therapy for patients with less severe HF. During the 35th annual meeting of the International Society for Heart & Lung Transplantation in Nice, France, Pagani et al[72] presented results from the multicenter destination study ENDURANCE (Prospective, Randomized, Controlled, Unblinded, Multi-Center Clinical Trial to Evaluate the HeartWare® Ventricular Assist System [VAS] for Destination Therapy of Advanced Heart Failure), which prospectively evaluated event-free 2-year survival of patients with HF who had NYHA class IIIB to IV symptoms and underwent implantation of a HeartWare or an HM II device, with comparable primary end points of 67.6% vs 60.2%, respectively (P=.17). However, the combined hemorrhagic/ischemic stroke rate for the HeartWare device was 31.1% compared with 12.7% for the HM II.[72] The National Heart, Lung, and Blood Institute has initiated the Randomized Evaluation of VAD Intervention Before Inotropic Therapy study (REVIVE-IT) as a randomized trial comparing the effectiveness of the HM II to optimal medical therapy in NYHA class III patients (INTERMACS 7) with illness not severe enough to qualify for transplant or permanent LVAD therapy based on current guidelines. In addition to survival benefits, functional improvement measured by 6-minute walk distance, and quality of life measures (freedom from major disabling stroke) will be evaluated.[73] The 2015 annual meeting of the International Society for Heart & Lung Transplantation offered preliminary results from a similar prospective, nonrandomized observational study, ROADMAP (Randomized Olmesartan and Diabetes Microalbuminuria Prevention). That study focused on patients in NYHA class IIIB and ambulatory class IV (INTERMACS 4-6) and documented higher survival at 1 year, better functional capacity, and higher quality of life in patients who received LVAD support compared with optimal medical therapy, although at a cost of increased composite adverse events risk.[74] Another pilot screening trial, the MedaMACS (Medical Arm of Mechanically Assisted Circulatory Support) study, should leverage the power of observation research to guide patient-centered decisions about mechanical circulatory support.[75]

LVAD AS BTT

Heart transplant remains an optimal treatment in advanced chronic HF. Recipients of HTx have a higher survival rate and report a better quality of life despite advances in mechanical support devices.[76] Studies have reported 1-year survival rates of 90% and 10-year survival rates of 60% after HTx. Studies also have found that 95% of HTx recipients remain symptom free with minimal activity limitations,[41] and 50% of patients survive beyond 11 years.[76] The advent of CF-LVADs and improved LVADs likely resulted in closing this gap.[41,76,77] The aim of BTT is to successfully bridge patients with end-stage HF to HTx.

Trials have found that LVAD support is a successful BTT therapy. The use of LVADs as BTT has nearly tripled, from 8.4% in the early 1990s to 22.8% in 2005, and the 1-year survival on the HTx waiting list has improved from 49.5% to 69%.[15] A recent post-FDA approval study evaluating the HM II for BTT in the United States reported that 79% of 281 patients had received a transplant, recovered cardiac function and underwent device explantation, or remained on LVAD support at 18 months.[18] The overall survival rate with CF-LVAD support was 82% at 6 months, 73% at 1 year, and 72% at 18 months. Of the 157 patients who underwent HTx, the post-transplant survival rate was 96% at 30 days and 86% at 1 year. Additionally, NYHA class, exercise capacity, and quality of life improved with LVAD support.

Baseline creatinine value predicts survival with LVADs (Figure 4), but the device implant itself improves end-organ function, potentially enhancing survival and improving transplant outcomes[50,78,79] as defined by Lietz et al, "end-organ function as a determinant of success with the LVAD."[50] Indeed, end-organ function has been noted to be improved for up to 15 months in retrospective studies,[80] and anecdotal reports indicate that patients with LVAD support can have preservation of end-organ function for more than 5 years.[17]

Inotropic therapy remains an alternative option to support patients while waiting for

Mayo Clin Proc. ■ July 2016;91(7):927-940 ■ http://dx.doi.org/10.1016/j.mayocp.2016.05.002
www.mayoclinicproceedings.org

transplant, and controversy remains regarding when to use LVAD or inotropic therapy. A previous single-center study evaluated the 1-year posttransplant survival rate in patients bridged with milrinone and in those initially bridged with milrinone and subsequently requiring LVAD support.[81] The second group, which was by definition more compromised, had a longer waiting time and decreased survival. Furthermore, a report by Sasaki et al[82] suggests that 5-year outcomes posttransplant are similar between subjects bridged with LVAD or inotropic therapy. A recent study indicated that although posttransplant survival may be slightly better than with inotropic therapy alone, the worst outcomes were observed among patients who underwent LVAD implantation after initial inotropic therapy failed.[83] In addition, survival to transplant was better with LVAD support. The LVAD group had higher immunosensitization, likely related to higher rates of blood transfusion, than the inotrope-supported group. Interestingly, the LVAD group, for unclear reasons, had less chronic rejection than the inotrope-supported group. No difference was noted between groups in acute rejection, posttransplant infection, or revascularization rates.[83] Review of the INTERMACS database suggests 78% survival with transplant, ongoing LVAD support, or recovery at 6 months post-LVAD implant.[84] These data in aggregate suggest that LVAD can be utilized successfully as a BTT strategy. Our institution favors LVAD support as BTT in patients with long projected wait times, a history of severe ventricular arrhythmias, substantial hemodynamic compromise, and end-organ dysfunction.

LVAD AS DT

An exciting development is the potential to utilize LVAD support for extended periods of time in patients not eligible for HTx. The HM II DT trial was designed to compare survival between the HM II and the HM XVE.[85] The results were reported in 2009 and documented improved survival at 2 years with the HM II, which was subsequently approved for DT.[24,85] The Table presents the actual survival results of 247 DT patients reported by Jorde et al[51] in 2014.

It should also be noted that the DT strategy raises issues regarding the potential discontinuation of LVAD support. This discussion of when to discontinue LVAD support has been controversial. Members of our group, in collaboration with colleagues in the palliative medicine field, have proposed parameters for the appropriateness of discontinuation of LVAD support and to ensure that patients receiving LVADs as DT are aware of palliative options as an alternative to device implant.[86]

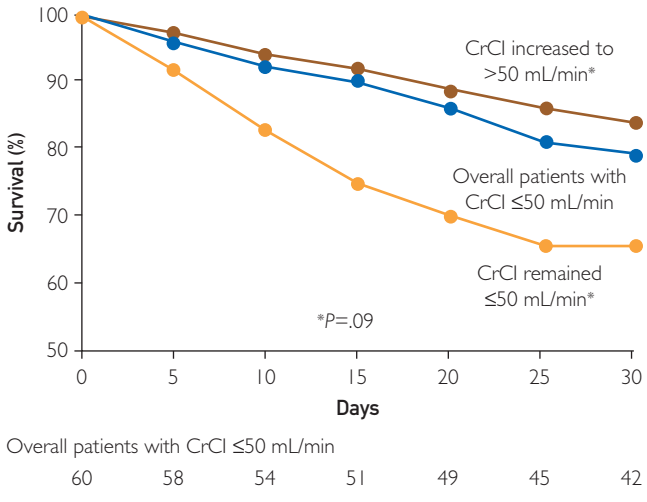

FIGURE 4. Thirty-day survival for patients with baseline creatinine clearance (CrCl) of 50 mL/min per 1.73 m^2 or less (to convert to mL/s per m^2, multiply by 0.0167), stratified by recovery after left ventricular assist device implantation. Patients whose CrCl recovered to more than 50 mL/min per 1.73 m^2 had higher 30-day postimplant survival. From *Ann Thorac Surg*,[78] with permission.

LVAD AS A BRIDGE TO DECISION

An LVAD can be used as a bridge to decision in patients initially unsuitable for transplant listing. These patients may have improvement in certain physiologic parameters such as pulmonary hypertension after LVAD implant or gain enough malignancy-free time to be considered for transplant. Interestingly, one study reported that among patients not deemed to be suitable transplant candidates by standard listing criteria, LVAD therapy as a DT strategy has better outcomes than utilization of extended listing criteria.[87]

COMPLICATIONS RELATED TO LVAD THERAPY

Gastrointestinal Tract Bleeding

Recently, there have been reports of an increased rate of nonsurgical bleeding among

TABLE. Kaplan-Meier Survival for the Destination Therapy Population of the HeartMate II LVAD Based on the INTERMACS Profile

INTERMACS profile	Survival at 1 year	Survival at 2 years
1-3 (n=184)	72%±3%	60%±4%
4-7 (n=63)	82%±5%	69%±6%

INTERMACS = Interagency Registry for Mechanically Assisted Circulatory Support; LVAD = left ventricular assist device. Data from J Am Coll Cardiol.[51]

CF-LVAD recipients, with a gastrointestinal (GI) tract bleeding rate of 63 per 100 patient-years compared with the very low rate of 6.8 per 100 patient-years in PF-LVAD recipients.[88] In light of this report, determining the potential causes and risk factors for the development of bleeding complications is essential to improve overall outcomes as well as the quality of life of LVAD recipients.

One explanation for the high GI tract bleeding rate among CF-LVAD recipients is a proposed theory of acquired von Willebrand syndrome (AvWS) secondary to mechanical damage within the pump. It is believed that the rotating components of CF-LVADs may cause von Willebrand factor (vWF) deformity and subsequent cleavage of the high-molecular-weight multimers into smaller ones that are cleared from the bloodstream, resulting in the loss or reduction of the large vWF multimers that are essential for promoting platelets. The result is that previously asymptomatic patients with GI tract and nasal angiodysplasias would have impaired platelet-mediated hemostasis, leading to more bleeding.[89] Reporting on a cohort of 37 CF-LVAD recipients, Crow et al[89] noted that although all patients had development of AvWS after LVAD implantation, not all of them had bleeding complications. The patients with bleeding had significantly higher levels of vWF antigen, ristocetin cofactor, and collagen-binding capacity measured before LVAD implantation as well as 30 days postimplant. These findings suggest that AvWS alone is not sufficient for development of bleeding complications after CF-LVAD implantation and that high-molecular-weight vWF multimer levels are not the only predictive marker for this complication.[89]

Other factors contributing to bleeding may be the anticoagulant use in CF-LVAD recipients (patients in whom PF-LVADs were implanted did not receive warfarin because of conflicting data), degree of inflammatory response,[90] presence of angiodysplasia, and possibly blood group type.[89] At our centers, we use warfarin as an anticoagulant, with an international normalized ratio (INR) goal range of 2.0 to 3.0, along with antiplatelet therapy and aspirin at 81 to 325 mg/d as proposed by recent guidelines.[19] We have also reported our experience with successful management of patients with GI tract bleeding without the use of warfarin.[91] The effects of next-generation antiplatelet and anticoagulation medications (thienopyridines, factor Xa, and direct thrombin inhibitors) have not been studied in the LVAD population, and thus their effect on bleeding complications in this population remains undefined and may be an area for future investigations.

Pump Thrombosis

Despite the recommended therapy of a combination of antiplatelet and anticoagulation therapy in CF-LVAD recipients, there was a 6-fold increase in the rates of reported pump thrombosis in 2011-2012, and the freedom from pump exchange or death from thrombosis decreased from 99% at 6 months in 2008-2009 to 94% in 2012.[73] Starling et al[92] reported a 12.2% incidence of confirmed or suspected pump thrombosis in a multicenter cohort of 837 patients. Considerable controversy exists regarding the most reliable methods for the detection of pump thrombus; clinical signs of hemolysis are often the early indicators of pump thrombus, particularly if associated with increased pump power utilization.[93] Echocardiography has proven useful in detecting pump thrombosis, particularly with associated reduction in diastolic flow velocity across the cannula and increased systolic to diastolic flow velocity ratio.[94,95] Cardiovascular computed tomography may be more reliable, with reported sensitivity of 85% and specificity approaching 100%.[96] Several risk factors for pump thrombosis have been identified: recent implantation, marked elevation of lactate dehydrogenase level at 1 month postimplant, young age, declining renal function, large stature, and less severe ventricular dysfunction.[73] One possible explanation for the increased rate of pump thrombosis may be inadequate antiplatelet or anticoagulation therapy. Indeed,

Mayo Clin Proc. ■ July 2016;91(7):927-940 ■ http://dx.doi.org/10.1016/j.mayocp.2016.05.002
www.mayoclinicproceedings.org

many patients with pump thrombosis have subtherapeutic INR levels or take a low dose of aspirin because of either poor adherence or concern about bleeding complications.

Another possible explanation for thrombosis could be reduced blood flow across the pump caused by lower pump speed, aortic regurgitation, arrhythmias, kinking of the inflow graft, and hypovolemia. The increased rate of thrombosis has significant consequences on patient outcomes, with higher mortality in those undergoing pump exchange for thrombosis along with a greater incidence of neurologic-related and infection-related morbidity in survivors of pump exchanges.[73] Clinically suspected pump thrombosis may be managed medically with intravenous anticoagulation therapy, thrombolytic agents, and antiplatelet therapy or surgically with pump replacement or explantation or urgent HTx for eligible patients.[92] Stulak and Maltais[97] reported a peak in the incidence of pump thrombosis in 2012 with a significant decrease in 2013, suggesting a possible association with adoption of less intense anticoagulation strategies (INR, 1.5-2.0) beginning in 2009 for HM II LVADs. Currently presented preliminary analysis of 90-day outcomes data from the prospective PREVENT (Prevention of HeartMate II Pump Thrombosis) study revealed an incidence of 1% for confirmed and 2% for suspected thrombosis in patients with a median INR of 2.2 (goal INR, 2.0-2.5) with rapid initiation of warfarin and aspirin therapy. Overall Kaplan-Meier survival was 93%.[98] Although pump thrombosis remains uncommon, further studies are needed to improve prevention, identification, and treatment for this potentially catastrophic complication of durable CF-LVAD.

Right-Sided HF After LVAD Implantation

Dysfunction of the RV remains a challenge after LVAD implantation. Risk factors for RV dysfunction after LVAD implantation include preoperative markers of end-organ dysfunction, including renal or hepatic dysfunction and anemia, in addition to echocardiographic parameters of RV dysfunction, elevated filling pressures, and need for intra-aortic balloon pump support preoperatively.[50,99,100] Nevertheless, LVAD therapy may improve RV hemodynamics and pulmonary hypertension, and younger patients can receive successful long-term LVAD therapy along with proper medical management to support the RV; thus, in experienced centers, RV dysfunction should not be considered an absolute contraindication to LVAD implantation.[101-103] It must be acknowledged that RV failure remains a major source of morbidity and mortality in the LVAD setting, and recent studies confirm that RV failure predicts poorer outcomes with LVAD therapy.[101-103] Although these patients have a poor prognosis and it is unlikely that they would do well with inotropic therapy alone, it remains to be demonstrated whether LVAD therapy can impact long-term outcomes among recipients with RV dysfunction.[101-103] In patients with severe biventricular failure, total artificial heart therapy has emerged as a modality for BTT.[104]

LVAD AS A BRIDGE TO RECOVERY

Left ventricular assist device therapy as a bridge to recovery remains a controversial topic. A working group on LVAD recovery found that although there is evidence that LVADs lead to echocardiographic and cellular improvement, there is little evidence to suggest that clinical recovery occurs in a meaningful proportion of patients.[105] The Harefield group, however, has reported sustained recovery with both PF and CF devices.[106,107] These studies followed aggressive protocols of titration with HF medications, pump weaning parameters, and utilization of the β-agonist growth-promoting agent clenbuterol to treat myocardial atrophy caused during LVAD support.[106] Clenbuterol, used to induce insulinlike growth factor 1 gene expression to stimulate physiologic hypertrophy in cultured cardiomyocytes in vitro, and possibly in vivo, has been reported to contribute to sustained myocardial recovery.[108] This remains an exciting area of ongoing investigation.

FUTURE DIRECTIONS

Although recent developments in LVAD technology have improved survival and quality of life among LVAD recipients, challenges remain. Studies are ongoing to develop strategies to make smaller and more durable devices, to diminish thrombosis, and to minimize surgical complication rates. A miniaturized LVAD requiring remarkably reduced surgical intervention might have the potential to extend the indications for earlier stages of HF. This

device does not require sternotomy, ventricular coring, or cardiopulmonary bypass.[109] A novel approach combining support of circulation with minimalistic surgery is presented by the Synergy Pocket Micro-pump device (CircuLite, Inc). Like a pacemaker, this device is placed through minithoracotomy in a right subclavicular subcutaneous pocket. The device provides blood flow of up to 3 L/min with the inflow cannula in the left atrium and the outflow cannula in the right subclavian artery. This support device has been proven to provide significant and steady improvement of many hemodynamic parameters.[110,111] Patients eagerly await technology that will allow for completely implantable devices.[112] Research continues to evaluate methods of providing variable flow in the LVAD setting and to develop automated modulation of flow with increased demand, as in exercise.[113]

Cell therapy strategies may create opportunities to advance cardiac recovery programs in the future.[114] Organized by the Cardiothoracic Surgical Trials Network in collaboration with the National Heart, Lung, and Blood Institute, prospective interventional trials investigating the safety and efficacy of injecting mesenchymal precursor cells (MPCs) into the heart during the LVAD implantation have been introduced. In 2014, Ascheim et al[115] reported a study of 30 patients randomized 2:1 to receive an intramyocardial injection of 25 million MPCs vs placebo during the LVAD implantation procedure. At 90 days after implant, successful temporary weaning (defined as a transient reduction in pump speed) was achieved in 50% of the patients who received MPCs and in 20% of the control patients, although at 12 months, 30% of the MPC patients and 40% of the control patients were successfully temporarily weaned from LVAD support (P=.69). This preliminary trial proved intramyocardial injection of MPCs to be safe and revealed a potential for efficacy.[115] A second phase of the trial, primarily focused on functional status defined by the number of temporary weans from LVAD support tolerated over the 6 months postrandomization, has recently opened enrollment. A successful wean is considered the ability to tolerate temporary weaning from LVAD support for 30 minutes without sustained symptoms of worsening HF.[116,117]

As noted previously, LVADs can be used in situations of refractory ventricular tachycardia/fibrillation and have the potential to substantially maintain circulation for certain periods of time.[43-45] It was reported that stem cells that derived cardiomyocytes could also mitigate ventricular tachycardia if they were transplanted in slow conduction areas of reentrant circuits.[7,118-120] These data support the safety of combining MCS and stem cell technology, which might potentially further reduce the risk of fatal arrhythmia.[118] Thus, the field of LVAD therapy in particular, and mechanical assist support in general, remains an area of promising multidisciplinary collaboration in the foreseeable future.

CONCLUSION

Left ventricular assist device support has revolutionized advanced HF treatment as a very effective BTT therapy and most recently as a DT strategy, with newer devices allowing long-term treatment. Exciting areas of ongoing investigation include myocardial recovery with LVADs and transitioning patients not initially deemed to be transplant candidates to transplant eligibility with LVAD therapy. Although multiple challenges and complications remain, these therapies provide exciting opportunities for ongoing clinical and basic research in the LVAD field.

ACKNOWLEDGMENTS

We thank Hui Shan Chiew, MD, graduate of the Medical Faculty Hradec Kralove, Czech Republic, and Ms Zoe A. Malinchoc, Mayo Clinic, for their help in the preparation of the submitted manuscript.

Abbreviations and Acronyms: **AvWS** = acquired von Willebrand syndrome; **BTT** = bridge to transplant; **CF** = continuous flow; **DT** = destination therapy; **FDA** = Food and Drug Administration; **GI** = gastrointestinal; **HF** = heart failure; **HM** = HeartMate; **HTx** = heart transplant; **INR** = international normalized ratio; **INTERMACS** = Interagency Registry for Mechanically Assisted Circulatory Support; **LVAD** = left ventricular assist device; **MCS** = mechanical cardiac support; **MPC** = mesenchymal precursor cell; **NYHA** = New York Heart Association; **PF** = pulsatile flow; **RV** = right ventricular; **vWF** = von Willebrand factor

Grant Support: This work was supported by the European Regional Development Fund — Project FNUSA-ICRC (No. CZ.1.05/1.1.00/02.0123).

Correspondence: Address to John A. Schirger, MD, Division of Cardiovascular Diseases, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (schirger.john@mayo.edu).

REFERENCES

1. Levy D, Kenchaiah S, Larson MG, et al. Long-term trends in the incidence of and survival with heart failure. *N Engl J Med*. 2002;347(18):1397-1402.
2. Candrilli SD, Kuznik A, Mendys PM, Wilson DJ. Prevalence and coexistence of cardiovascular comorbidities among the US dyslipidemic population aged ≥ 65 years by lipid-lowering medication use status. *Postgrad Med*. 2010;122(5):142-149.
3. Ahn SA, Jong P, Yusuf S, Bangdiwala SI, Pouleur HG, Rousseau MF. Early versus delayed enalapril in patients with left ventricular systolic dysfunction: impact on morbidity and mortality 15 years after the SOLVD trial [letter]. *J Am Coll Cardiol*. 2006;47(9):1904-1905.
4. Otterstad JE, Ford I. The effect of carvedilol in patients with impaired left ventricular systolic function following an acute myocardial infarction: how do the treatment effects on total mortality and recurrent myocardial infarction in CAPRICORN compare with previous beta-blocker trials? *Eur J Heart Fail*. 2002;4(4):501-506.
5. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet*. 2001;357(9266):1385-1390.
6. Tang AS, Wells GA, Talajic M, et al; Resynchronization-Defibrillation for Ambulatory Heart Failure Trial Investigators. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med*. 2010;363(25):2385-2395.
7. Levy WC, Mozaffarian D, Linker DT, Farrar DJ, Miller LW; REMATCH Investigators. Can the Seattle Heart Failure Model be used to risk-stratify heart failure patients for potential left ventricular assist device therapy? *J Heart Lung Transplant*. 2009;28(3):231-236.
8. Kuppahally SS, Valantine HA, Weisshaar D, et al. Outcome in cardiac recipients of donor hearts with increased left ventricular wall thickness. *Am J Transplant*. 2007;7(10):2388-2395.
9. Rose EA, Gelijns AC, Moskowitz AJ, et al; Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) Study Group. Long-term use of a left ventricular assist device for end-stage heart failure. *N Engl J Med*. 2001;345(20):1435-1443.
10. Rogers JG, Aaronson KD, Boyle AJ, et al; HeartMate II Investigators. Continuous flow left ventricular assist device improves functional capacity and quality of life of advanced heart failure patients. *J Am Coll Cardiol*. 2010;55(17):1826-1834.
11. Park SJ, Tector A, Piccioni W, et al. Left ventricular assist devices as destination therapy: a new look at survival. *J Thorac Cardiovasc Surg*. 2005;129(1):9-17.
12. Patel CB, Alexander KM, Rogers JG. Mechanical circulatory support for advanced heart failure. *Curr Treat Options Cardiovasc Med*. 2010;12(6):549-565.
13. Zimpfer D, Zrunek P, Sandner S, et al. Post-transplant survival after lowering fixed pulmonary hypertension using left ventricular assist devices. *Eur J Cardiothorac Surg*. 2007;31(4):698-702.
14. Pagani FD, Miller LW, Russell SD, et al; HeartMate II Investigators. Extended mechanical circulatory support with a continuous-flow rotary left ventricular assist device. *J Am Coll Cardiol*. 2009;54(4):312-321.
15. Lietz K, Miller LW. Improved survival of patients with end-stage heart failure listed for heart transplantation: analysis of organ procurement and transplantation network/U.S. United Network of Organ Sharing data, 1990 to 2005. *J Am Coll Cardiol*. 2007;50(13):1282-1290.
16. Slaughter MS, Meyer AL, Birks EJ. Destination therapy with left ventricular assist devices: patient selection and outcomes. *Curr Opin Cardiol*. 2011;26(3):232-236.
17. Starling RC, Naka Y, Boyle AJ, et al. Results of the post-U.S. Food and Drug Administration-approval study with a continuous flow left ventricular assist device as a bridge to heart transplantation: a prospective study using the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) [published correction appears in *J Am Coll Cardiol*. 2011;58(20):2142]. *J Am Coll Cardiol*. 2011;57(19):1890-1898.
18. Aggarwal S, Pagani FD. Bridge to transplantation: current outcomes. *J Card Surg*. 2010;25(4):455-461.
19. Feldman D, Pamboukian SV, Teuteberg JJ, et al. The 2013 International Society for Heart and Lung Transplantation Guidelines for mechanical circulatory support: executive summary. *J Heart Lung Transplant*. 2013;32(2):157-187.
20. Slaughter MS, Pagani FD, Rogers JG, et al; HeartMate II Clinical Investigators. Clinical management of continuous-flow left ventricular assist devices in advanced heart failure. *J Heart Lung Transplant*. 2010;29(4, suppl):S1-S39.
21. Slaughter MS, Rogers JG, Milano CA, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. *N Engl J Med*. 2009;361(23):2241-2251.
22. Frazier OH, Rose EA, Oz MC, et al; HeartMate LVAS Investigators. Multicenter clinical evaluation of the HeartMate vented electric left ventricular assist system in patients awaiting heart transplantation. *J Thorac Cardiovasc Surg*. 2001;122(6):1186-1195.
23. Dembitsky WP, Tector AJ, Park S, et al. Left ventricular assist device performance with long-term circulatory support: lessons from the REMATCH trial. *Ann Thorac Surg*. 2004;78(6):2123-2129.
24. Wieselthaler GM, O'Driscoll G, Jansz P, Khaghani A, Strueber M; HVAD Clinical Investigators. Initial clinical experience with a novel left ventricular assist device with a magnetically levitated rotor in a multi-institutional trial. *J Heart Lung Transplant*. 2010;29(11):1218-1225.
25. Wu L, Weng YG, Dong NG, et al. Outcomes of HeartWare Ventricular Assist System support in 141 patients: a single-centre experience. *Eur J Cardiothorac Surg*. 2013;44(1):139-145.
26. Slaughter MS. Implantation of the HeartWare left ventricular assist device. *Semin Thorac Cardiovasc Surg*. 2011;23(3):245-247.
27. Krabatsch T, Hennig E, Stepanenko A, et al. Evaluation of the HeartWare HVAD centrifugal pump for right ventricular assistance in an in vitro model. *ASAIO J*. 2011;57(3):183-187.
28. Strueber M, Larbalestier R, Jansz P, et al. Results of the post-market Registry to Evaluate the HeartWare Left Ventricular Assist System (ReVOLVE). *J Heart Lung Transplant*. 2014;33(5):486-491.
29. Mussivand T, Hetzer R, Vitali E, et al. Clinical results with an ePTFE inflow conduit for mechanical circulatory support. *J Heart Lung Transplant*. 2004;23(12):1366-1370.
30. Cheng A, Williamitis CA, Slaughter MS. Comparison of continuous-flow and pulsatile-flow left ventricular assist devices: is there an advantage to pulsatility? *Ann Cardiothorac Surg*. 2014;3(6):573-581.
31. Hall JL, Fermin DR, Birks EJ, et al. Clinical, molecular, and genomic changes in response to a left ventricular assist device. *J Am Coll Cardiol*. 2011;57(6):641-652.
32. Maltais S, Jaik NP, Feurer ID, et al. Mechanical circulatory support and heart transplantation: donor and recipient factors influencing graft survival. *Ann Thorac Surg*. 2013;96(4):1252-1258.
33. Thacher T, Gambillara V, da Silva RF, Silacci P, Stergiopulos N. Reduced cyclic stretch, endothelial dysfunction, and oxidative

stress: an ex vivo model. *Cardiovasc Pathol*. 2010;19(4):e91-e98.
34. Baba A, Dobsak P, Mochizuki S, et al. Evaluation of pulsatile and nonpulsatile flow in microvessels of the bulbar conjunctiva in the goat with an undulation pump artificial heart. *Artif Organs*. 2003;27(10):875-881.
35. Sezai A, Shiono M, Orime Y, et al. Major organ function under mechanical support: comparative studies of pulsatile and nonpulsatile circulation. *Artif Organs*. 1999;23(3):280-285.
36. Presson RG Jr, Baumgartner WA Jr, Peterson AJ, Glenny RW, Wagner WW Jr. Pulmonary capillaries are recruited during pulsatile flow. *J Appl Physiol (1985)*. 2002;92(3):1183-1190.
37. Ootaki C, Yamashita M, Ootaki Y, et al. Reduced pulsatility induces periarteritis in kidney: role of the local renin-angiotensin system. *J Thorac Cardiovasc Surg*. 2008;136(1):150-158.
38. Netuka I, Sood P, Pya Y, et al. Fully magnetically levitated left ventricular assist system for treating advanced Hf: a multicenter study. *J Am Coll Cardiol*. 2015;66(23):2579-2589.
39. Jessup M, Abraham WT, Casey DE, et al. 2009 Focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines; developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation*. 2009;119(14):1977-2016.
40. Peura JL, Colvin-Adams M, Francis GS, et al; American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology; Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; Council on Cardiovascular Disease in the Young; Council on Cardiovascular Nursing; Council on Cardiovascular Radiology and Intervention; and Council on Cardiovascular Surgery and Anesthesia. Recommendations for the use of mechanical circulatory support: device strategies and patient selection; a scientific statement from the American Heart Association. *Circulation*. 2012;126(22):2648-2667.
41. Lund LH, Matthews J, Aaronson K. Patient selection for left ventricular assist devices. *Eur J Heart Fail*. 2010;12(5):434-443.
42. Wilson SR, Mudge GH Jr, Stewart GC, Givertz MM. Evaluation for a ventricular assist device: selecting the appropriate candidate. *Circulation*. 2009;119(16):2225-2232.
43. Oz MC, Rose EA, Slater J, Kuiper JJ, Catanese KA, Levin HR. Malignant ventricular arrhythmias are well tolerated in patients receiving long-term left ventricular assist devices. *J Am Coll Cardiol*. 1994;24(7):1688-1691.
44. Guerra F, Flori M, Bonelli P, Patani F, Capucci A. Electrical storm and heart failure worsening in implantable cardiac defibrillator patients. *Europace*. 2015;17(2):247-254.
45. Verma A, Kilicaslan F, Marrouche NF, et al. Prevalence, predictors, and mortality significance of the causative arrhythmia in patients with electrical storm. *J Cardiovasc Electrophysiol*. 2004;15(11):1265-1270.
46. Topilsky Y, Pereira NL, Shah DK, et al. Left ventricular assist device therapy in patients with restrictive and hypertrophic cardiomyopathy. *Circ Heart Fail*. 2011;4(3):266-275.
47. Joyce DL, Crow SS, John R, et al. Mechanical circulatory support in patients with heart failure secondary to transposition of the great arteries. *J Heart Lung Transplant*. 2010;29(11):1302-1305.
48. Alba AC, Rao V, Ivanov J, Ross HJ, Delgado DH. Usefulness of the INTERMACS scale to predict outcomes after mechanical assist device implantation. *J Heart Lung Transplant*. 2009;28(8):827-833.
49. Kirklin JK, Naftel DC, Pagani FD, et al. Sixth INTERMACS annual report: a 10,000-patient database. *J Heart Lung Transplant*. 2014;33(6):555-564.
50. Lietz K, Long JW, Kfoury AG, et al. Outcomes of left ventricular assist device implantation as destination therapy in the post-REMATCH era: implications for patient selection. *Circulation*. 2007;116(5):497-505.
51. Jorde UP, Kushwaha SS, Tatooles AJ, et al. Results of the destination therapy post-Food and Drug Administration approval study with a continuous flow left ventricular assist device: a prospective study using the INTERMACS registry (Interagency Registry for Mechanically Assisted Circulatory Support). *J Am Coll Cardiol*. 2014;63(17):1751-1757.
52. Lietz K, Miller LW. Patient selection for left-ventricular assist devices. *Curr Opin Cardiol*. 2009;24(3):246-251.
53. Altimir S, Lupón J, González B, et al. Sex and age differences in fragility in a heart failure population. *Eur J Heart Fail*. 2005;7(5):798-802.
54. Welsby IJ, Um J, Milano CA, Ortel TL, Arepally G. Plasmapheresis and heparin reexposure as a management strategy for cardiac surgical patients with heparin-induced thrombocytopenia. *Anesth Analg*. 2010;110(1):30-35.
55. Schaffer JM, Arnaoutakis GJ, Allen JG, et al. Bleeding complications and blood product utilization with left ventricular assist device implantation. *Ann Thorac Surg*. 2011;91(3):740-747.
56. Holdy K, Dembitsky W, Eaton LL, et al. Nutrition assessment and management of left ventricular assist device patients. *J Heart Lung Transplant*. 2005;24(10):1690-1696.
57. Zahr F, Genovese E, Mathier M, et al. Obese patients and mechanical circulatory support: weight loss, adverse events, and outcomes. *Ann Thorac Surg*. 2011;92(4):1420-1426.
58. Coyle LA, Ising MS, Gallagher C, et al. Destination therapy: one-year outcomes in patients with a body mass index greater than 30. *Artif Organs*. 2010;34(2):93-97.
59. Brewer RJ, Lanfear DE, Sai-Sudhakar CB, et al. Extremes of body mass index do not impact mid-term survival after continuous-flow left ventricular assist device implantation. *J Heart Lung Transplant*. 2012;31(2):167-172.
60. Miller LW, Guglin M. Patient selection for ventricular assist devices: a moving target. *J Am Coll Cardiol*. 2013;61(12):1209-1221.
61. Park SJ, Liao KK, Segurola R, Madhu KP, Miller LW. Management of aortic insufficiency in patients with left ventricular assist devices: a simple coaptation stitch method (Park's stitch). *J Thorac Cardiovasc Surg*. 2004;127(1):264-266.
62. De Praetere H, Jacobs S, Rega F, Droogne W, Meyns B. Can a central stitch over the Arantius' nodules provide a solution for preoperative severe native AI in LVAD patients. *Int J Artif Organs*. 2013;36(3):220-224.
63. Deo SV, Hasin T, Altarabsheh SE, et al. Concomitant tricuspid valve repair or replacement during left ventricular assist device implant demonstrates comparable outcomes in the long term. *J Card Surg*. 2012;27(6):760-766.
64. University of Washington. Seattle Heart Failure Model. Universit of Washington website. http://depts.washington.edu/shfm/. Accessed March 23, 2015.
65. Koelling TM, Joseph S, Aaronson KD. Heart Failure Survival Score continues to predict clinical outcomes in patients with heart failure receiving beta-blockers. *J Heart Lung Transplant*. 2004;23(12):1414-1422.
66. Levy WC, Mozaffarian D, Linker DT, et al. The Seattle Heart Failure Model: prediction of survival in heart failure. *Circulation*. 2006;113(11):1424-1433.
67. Lee DS, Austin PC, Rouleau JL, Liu PP, Naimark D, Tu JV. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. *JAMA*. 2003;290(19):2581-2587.
68. Senni M, Santilli G, Parrella P, et al. A novel prognostic index to determine the impact of cardiac conditions and co-morbidities on one-year outcome in patients with heart failure. *Am J Cardiol*. 2006;98(8):1076-1082.
69. Metra M, Ponikowski P, Dickstein K, et al; Heart Failure Association of the European Society of Cardiology. Advanced chronic heart failure: a position statement from the Study Group on Advanced Heart Failure of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2007;9(6-7):684-694.

70. Pocock SJ, McMurray JV, Dobson J, et al. Weight loss and mortality risk in patients with chronic heart failure in the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) programme. *Eur Heart J*. 2008;29(21):2641-2650.
71. Jaarsma T, Beattie JM, Ryder M, et al; Advanced Heart Failure Study Group of the HFA of the ESC. Palliative care in heart failure: a position statement from the palliative care workshop of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2009;11(5):433-443.
72. Pagani FD, Milano CA, Tatooles AJ, et al. HeartWare HVAD for the treatment of patients with advanced heart failure ineligible for cardiac transplantation: results of the ENDURANCE Destination Therapy Trial. *J Heart Lung Transplant*. 2015;34(4, suppl):S9.
73. Kirklin JK, Naftel DC, Kormos RL, et al. Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) analysis of pump thrombosis in the HeartMate II left ventricular assist device. *J Heart Lung Transplant*. 2014;33(1):12-22.
74. Rogers JG, Boyle AJ, O'Connell JB, et al. Risk assessment and comparative effectiveness of left ventricular assist device and medical management in ambulatory heart failure patients: design and rationale of the ROADMAP clinical trial. *Am Heart J*. 2015;169(2):205-210.e20.
75. Stewart GC, Stevenson LW. INTERMACS and MedaMACS: how will they guide future therapy? *Curr Cardiol Rep*. 2013;15(9):394.
76. Mancini D, Lietz K. Selection of cardiac transplantation candidates in 2010. *Circulation*. 2010;122(2):173-183.
77. Aurora P, Edwards LB, Christie J, et al. Registry of the International Society for Heart and Lung Transplantation: eleventh official pediatric lung and heart/lung transplantation report—2008. *J Heart Lung Transplant*. 2008;27(9):978-983.
78. Butler J, Geisberg C, Howser R, et al. Relationship between renal function and left ventricular assist device use. *Ann Thorac Surg*. 2006;81(5):1745-1751.
79. Slaughter MS. Long-term continuous flow left ventricular assist device support and end-organ function: prospects for destination therapy. *J Card Surg*. 2010;25(4):490-494.
80. Radovancevic B, Vrtovec B, de Kort E, Radovancevic R, Gregoric ID, Frazier OH. End-organ function in patients on long-term circulatory support with continuous- or pulsatile-flow assist devices. *J Heart Lung Transplant*. 2007;26(8):815-818.
81. Assad-Kottner C, Chen D, Jahanyar J, et al. The use of continuous milrinone therapy as bridge to transplant is safe in patients with short waiting times. *J Card Fail*. 2008;14(10):839-843.
82. Sasaki H, Mitchell JD, Jessen ME, et al. Bridge to heart transplantation with left ventricular assist device versus inotropic agents in status 1 patients. *J Card Surg*. 2009;24(6):756-762.
83. Wozniak CJ, Stehlik J, Baird BC, et al. Ventricular assist devices or inotropic agents in status 1A patients? survival analysis of the United Network of Organ Sharing database. *Ann Thorac Surg*. 2014;97(4):1364-1371.
84. Holman WL, Kormos RL, Naftel DC, et al. Predictors of death and transplant in patients with a mechanical circulatory support device: a multi-institutional study. *J Heart Lung Transplant*. 2009;28(1):44-50.
85. Lietz K. Destination therapy: patient selection and current outcomes. *J Card Surg*. 2010;25(4):462-471.
86. Swetz KM, Freeman MR, AbouEzzeddine OF, et al. Palliative medicine consultation for preparedness planning in patients receiving left ventricular assist devices as destination therapy. *Mayo Clin Proc*. 2011;86(6):493-500.
87. Daneshmand MA, Rajagopal K, Lima B, et al. Left ventricular assist device destination therapy versus extended criteria cardiac transplant. *Ann Thorac Surg*. 2010;89(4):1205-1209.
88. Crow S, Milano C, Joyce L, et al. Comparative analysis of von Willebrand factor profiles in pulsatile and continuous left ventricular assist device recipients. *ASAIO J*. 2010;56(5):441-445.
89. Crow S, Chen D, Milano C, et al. Acquired von Willebrand syndrome in continuous-flow ventricular assist device recipients. *Ann Thorac Surg*. 2010;90(4):1263-1269.
90. Klovaite J, Gustafsson F, Mortensen SA, Sander K, Nielsen LB. Severely impaired von Willebrand factor-dependent platelet aggregation in patients with a continuous-flow left ventricular assist device (HeartMate II). *J Am Coll Cardiol*. 2009;53(23):2162-2167.
91. Pereira NL, Chen D, Kushwaha SS, Park SJ. Discontinuation of antithrombotic therapy for a year or more in patients with continuous-flow left ventricular assist devices. *Interact Cardiovasc Thorac Surg*. 2010;11(4):503-505.
92. Starling RC, Moazami N, Silvestry SC, et al. Unexpected abrupt increase in left ventricular assist device thrombosis. *N Engl J Med*. 2014;370(1):33-40.
93. Shah P, Mehta VM, Cowger JA, Aaronson KD, Pagani FD. Diagnosis of hemolysis and device thrombosis with lactate dehydrogenase during left ventricular assist device support. *J Heart Lung Transplant*. 2014;33(1):102-104.
94. Uriel N, Morrison KA, Garan AR, et al. Development of a novel echocardiography ramp test for speed optimization and diagnosis of device thrombosis in continuous-flow left ventricular assist devices: the Columbia ramp study. *J Am Coll Cardiol*. 2012;60(18):1764-1775.
95. Fine NM, Topilsky Y, Oh JK, et al. Role of echocardiography in patients with intravascular hemolysis due to suspected continuous-flow LVAD thrombosis. *J Am Coll Cardiol Img*. 2013;6(11):1129-1140.
96. Mishkin JD, Enriquez JR, Meyer DM, et al. Utilization of cardiac computed tomography angiography for the diagnosis of left ventricular assist device thrombosis. *Circ Heart Fail*. 2012;5(2):e27-e29.
97. Stulak JM, Maltais S. A different perspective on thrombosis and the HeartMate II [letter]. *N Engl J Med*. 2014;370(15):1467-1468.
98. Emani S, Keebler M, Ransom JM, et al. Prevention of HeartMate II pump thrombosis - recommendations and preliminary observations from the PREVENT study [abstract]. *Circulation*. 2015;132:A16405.
99. Topilsky Y, Oh JK, Shah DK, et al. Echocardiographic predictors of adverse outcomes after continuous left ventricular assist device implantation. *J Am Coll Cardiol Img*. 2011;4(3):211-222.
100. Drakos SG, Janicki L, Horne BD, et al. Risk factors predictive of right ventricular failure after left ventricular assist device implantation. *Am J Cardiol*. 2010;105(7):1030-1035.
101. Liden H, Haraldsson A, Ricksten SE, Kjellman U, Wiklund L. Does pretransplant left ventricular assist device therapy improve results after heart transplantation in patients with elevated pulmonary vascular resistance? *Eur J Cardiothorac Surg*. 2009;35(6):1029-1034.
102. Baumwol J, Macdonald PS, Keogh AM, et al. Right heart failure and "failure to thrive" after left ventricular assist device: clinical predictors and outcomes. *J Heart Lung Transplant*. 2011;30(8):888-895.
103. Lee S, Kamdar F, Madlon-Kay R, et al. Effects of the HeartMate II continuous-flow left ventricular assist device on right ventricular function. *J Heart Lung Transplant*. 2010;29(2):209-215.
104. Kasirajan V, Tang DG, Katlaps GJ, Shah KB. The total artificial heart for biventricular heart failure and beyond. *Curr Opin Cardiol*. 2012;27(3):301-307.
105. Maybaum S, Mancini D, Xydas S, et al; LVAD Working Group. Cardiac improvement during mechanical circulatory support: a prospective multicenter study of the LVAD Working Group. *Circulation*. 2007;115(19):2497-2505.

106. Birks EJ, Tansley PD, Hardy J, et al. Left ventricular assist device and drug therapy for the reversal of heart failure. *N Engl J Med*. 2006;355(18):1873-1884.
107. Birks EJ, George RS, Hedger M, et al. Reversal of severe heart failure with a continuous-flow left ventricular assist device and pharmacological therapy: a prospective study. *Circulation*. 2011;123(4):381-390.
108. Barton PJ, Felkin LE, Birks EJ, et al. Myocardial insulin-like growth factor-1 gene expression during recovery from heart failure after combined left ventricular assist device and clenbuterol therapy. *Circulation*. 2005;112(9, suppl):I46-I50.
109. Slaughter MS, Giridharan GA, Tamez D, et al. Transapical miniaturized ventricular assist device: design and initial testing. *J Thorac Cardiovasc Surg*. 2011;142(3):668-674.
110. Meyns B, Klotz S, Simon A, et al. Proof of concept: hemodynamic response to long-term partial ventricular support with the synergy pocket micro-pump. *J Am Coll Cardiol*. 2009;54(1):79-86.
111. Meyns BP, Simon A, Klotz S, et al. Clinical benefits of partial circulatory support in New York Heart Association class IIIB and early class IV patients. *Eur J Cardiothorac Surg*. 2011;39(5):693-698.
112. Asgari SS, Bonde P. Implantable physiologic controller for left ventricular assist devices with telemetry capability. *J Thorac Cardiovasc Surg*. 2014;147(1):192-202.
113. Kishimoto Y, Takewa Y, Arakawa M, et al. Development of a novel drive mode to prevent aortic insufficiency during continuous-flow LVAD support by synchronizing rotational speed with heartbeat. *J Artif Organs*. 2013;16(2):129-137.
114. Fujita J, Itabashi Y, Seki T, et al. Myocardial cell sheet therapy and cardiac function. *Am J Physiol Heart Circ Physiol*. 2012;303(10):H1169-H1182.
115. Ascheim DD, Gelijns AC, Goldstein D, et al. Mesenchymal precursor cells as adjunctive therapy in recipients of contemporary left ventricular assist devices. *Circulation*. 2014;129(22):2287-2296.
116. Kron IL, LaPar DJ, Horvath KA; CTSN Investigators and the American Association for Thoracic Surgery Scientific Affairs and Government Relations Committee. Cardiothoracic Surgical Trials Network: evidence-based surgery [editorial]. *J Thorac Cardiovasc Surg*. 2016;151(1):28-29.
117. National Heart, Lung, and Blood Institute. Safety & Efficacy of Intramyocardial Injection of Mesenchymal Precursor Cells on Myocardial Function in LVAD Recipients. ClinicalTrials.gov identifier: NCT02362646. ClinicalTrials.gov website. https://clinicaltrials.gov/ct2/show/NCT02362646?term=NCT02362646&rank=1. Published February 9, 2015. Updated May 5, 2016. Accessed May 12, 2016.
118. Fujita S, Sano M. Treatment of the ventricular tachycardia with engraftment of pluripotent stem cells-derived cardiomyocytes [editorial]. *J Mol Cell Cardiol*. 2012;53(1):3-5.
119. Shiba Y, Fernandes S, Zhu WZ, Filice D, Muskheli V, Kim J, et al. Human ES-cell-derived cardiomyocytes electrically couple and suppress arrhythmias in injured hearts [letter]. *Nature*. 2012;489(7415):322-325.
120. Thompson SA, Burridge PW, Lipke EA, Shamblott M, Zambidis ET, Tung L. Engraftment of human embryonic stem cell derived cardiomyocytes improves conduction in an arrhythmogenic in vitro model. *J Mol Cell Cardiol*. 2012;53(1):15-23.