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STATE-OF-THE-ART PAPER

Patient Selection for Ventricular Assist Devices

A Moving Target

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The number of patients with advanced heart failure that has become unresponsive to conventional medical therapy is increasing rapidly. One of the most promising new alternatives to heart transplantation is use of ventricular assist devices (VADs). To date, there are no guidelines for appropriate selection for use of these devices that are approved by national societies in the field. This review addresses all of the general criteria for clinicians to keep in mind regarding when to refer a patient for evaluation and the specific issues addressed in patient selection. The field of mechanical circulatory support has advanced significantly over the past 10 years, resulting in rapid expansion of patients with advanced heart failure who can benefit from implantable devices. With progress of technology, limitations associated with age, body size, and comorbidities gradually become less prohibitive. The continuing simplification of design along with continued reduction in size of the devices, plus eventual elimination of the external drive line will make the use of VADs a superior option to heart transplant and even to medical management in many patients. We anticipate that the patient selection process outlined in the present review will continue to shift toward less advanced cases of heart failure. (J Am Coll Cardiol 2013;61:1209–21) © 2013 by the American College of Cardiology Foundation

No other field in cardiology is experiencing such explosive growth as mechanical circulatory support for advanced heart failure (HF). As increasing numbers of patients become refractory to optimized medical therapy, the need for definitive treatment modalities grow. Previously, the only proven treatment for these patients was heart transplantation. While the number of transplants has reached a plateau at 4,500 a year worldwide and 2,200 per year in the United States, growth in the number of recipients of long-term ventricular assist devices (VADs) is accelerating (Fig. 1). Estimates of potential recipients for VAD support vary widely, confounded by liberal use of definitions like "refractory HF," "advanced HF," and "stage D" HF, as well as changing indications for implantation. In some communities, the prevalence may be as low as 0.2% of the general HF population (1), while in others, it can be 3.1% of all adults (2). We estimate that the number of potential recipients for VAD support ranges from 150,000 to 250,000 (Fig. 2) (3).

There are published guidelines for patient selection for heart transplantation that are endorsed by most societies in the field, but there is much less guidance on selection of patients for mechanical support (4). The American Heart Association (AHA)/American College of Cardiology (ACC) guidelines for 2005, for example, recommended left VAD (LVAD) implantation as "reasonable in highly selected patients with refractory end-stage HF and an estimated 1-year mortality over 50% with medical therapy" (5). This text is unchanged in the 2009 update (6). There is one recent "best practice" document that includes both patient selection and clinical management of continuous flow LVADs (7).

There has been very little improvement in survival with medical treatment of advanced HF, with no new drugs shown to improve survival for over 10 years. In addition, we seem to be unable to alter disease progression once patients are hospitalized, as HF remains the greatest cause of readmission, with rates averaging over 20% at 1 month and 50% at 6 months. There are some tools to estimate survival in these patients (e.g., the Seattle Heart Failure model [8] and the Heart Failure Survival Score [9]), but none includes the number of hospitalizations, which is one of the most powerful predictors of survival (Fig. 3) (10). The previous New York Heart Association (NYHA) classification is very subjective and inconsistent, with large interobserver variability. This problem is further compounded by whether the patient is classified at the time of a hospital admission, typically as NYHA class IV, or 1 month after discharge, when they are much less symptomatic and may be considered class III. Not surprisingly, therefore, estimates for 1-year mortality in patients judged to have class IV or stage D HF range from 15% to 35%, as NYHA class IV or stage D HF includes those patients dependent on an inotropic agent

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Abbreviations and Acronyms

ALT = alanine aminotransferase
AST = aspartate aminotransferase
BUN = blood urea nitrogen
CVA = cerebrovascular accident
CVP = central venous pressure
HCT = hematocrit
OR = odds ratio
PAP = pulmonary arterial pressure
PCWP = pulmonary capillary wedge pressure
RAP = right atrial pressure
SVI = stroke volume index
TPG = transpulmonary gradient
WU = Wood unit(s)

in the hospital, as well as those who are symptom limited but are at home on oral medications (11). In contrast to the modest absolute increases in survival with medical therapy, even the first generation of LVAD, the pulsatile HeartMate I (Thoratec Corporation, Pleasanton, California), demonstrated the largest absolute improvement in survival (24% absolute and 100% relative increase compared to medical management) in an HF trial to date.

Introduction of the second-generation continuous flow LVAD, HeartMate II (Thoratec Corporation), increased survival to 68% at 1 year in a clinical trial of patients as a bridge to transplantation (12), and as has been shown in all published trials of LVADs to date, survival improved significantly to 85% in patients enrolled in the post-approval phase of the trial (13) and even higher in a nontrial experience with HeartMate II (14) (Fig. 4). Most recently, the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) trial of a third-generation continuous flow device, the Heartware (HeartWare, Framingham, MA), has reported 92% survival at 6 months in a clinical trial as a bridge to transplantation (Fig. 5). Importantly, the control arm in that study was from the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support), which showed nearly identical excellent survival in centers not involved in a prospective trial.

The very significant improvement in survival with the newer LVADs noted above is in large part because of the enormous improvement in device durability, with similar success now demonstrated with nearly all new continuous flow LVADs, which have only a single moving part and likely 10-year freedom from mechanical failure. This observation has re-emphasized that patient selection and timing of device implantation are the major determinants of success in the field of mechanical support for advanced HF.

Currently, VADs seem to be significantly underutilized. In a mere 10 years, design of the devices, implantation techniques, follow-up routines (15), and prognoses have changed dramatically. As they continue to change rapidly, so do the selection criteria for patients who can gain years of a quality life from mechanical circulatory support. Rapid growth in this field has exceeded the realization of these outcomes by many practicing clinicians. This report review the specific criteria to be used to decide when to consider referring a patient for LVAD therapy, with particular attention to those factors with the greatest impact on survival to hospital discharge and long term, as well as discussion of the controversy of age limit and severity of HF.

Indications for Mechanical Circulatory Support

There are three major often overlapping indications for the use of VADs: 1) as a bridge to transplantation for heart transplant candidates who are either "too sick" to wait for a donor to be identified because of severe acute, or acute-on-chronic HF, or have contraindications to transplantation, which are deemed to be transient; 2) as a lifelong support alternative for patients deemed ineligible for a heart transplantation, so-called destination therapy; and 3) as a bridge to myocardial recovery. A fourth term, bridge-to-a-bridge, is used for those patients who present with severe shock or following cardiac arrest and are supported with a temporary support VAD to see if they become candidates for a long-term support device.

Interestingly, the most common indication listed for 40% of all patients entered in the INTERMACS is bridge to decision. It is used when the best long-term option for a given patient is unclear at the time of LVAD implantation. For example, some patients for whom the initial intent was destination therapy may recover renal and hepatic function or have documented significant decrease in pulmonary hypertension and then become transplant candidates. Conversely, some patients who were originally listed as transplant candidates may be so satisfied with their quality of life on mechanical circulatory support that they elect to remain on the LVAD rather than undergo transplantation.

In part because of changes in the prioritization of transplant candidates to primarily status 1A, or the very sickest patients, an increasing number of patients are receiving

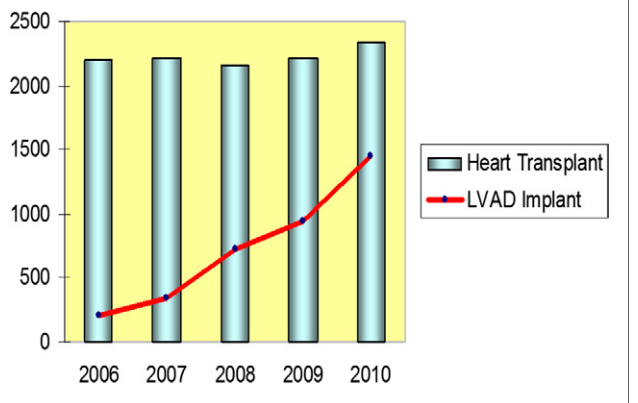

Figure 1 **Dynamics of the Heart Transplant and LVAD Implant Numbers in the United States 2006 to 2010**

While the number of transplants remains almost constant, there is accelerating growth in LVADs. Numbers for the graph are from INTERMACS and U.S. Department of Health and Human Services, respectively. Because INTERMACS statistics started in June 2006, we doubled the number of VADs for 2006.

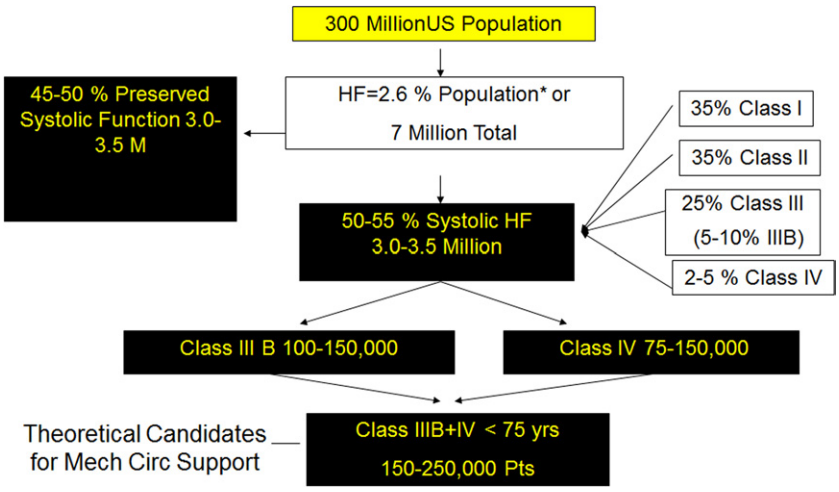

Figure 2 **Current Estimate of the Number of Advanced HF Patients**

This represents approximate number of potential VAD candidates. Data from Miller (3). HF = heart failure.

LVAD therapy at the time of transplantation because of either deterioration while on the transplant waiting list or are in refractory HF when first evaluated (3,10,16–18). Data from the ISHLT (International Society for Heart and Lung Transplantation) registry show that more than 33% of all patients undergo transplantation with an LVAD in place (17,18). This percentage varies greatly across the country to as high as 75% in programs where donor availability is low. Outcomes after transplantation are not different in those who were "bridged" with an LVAD compared with those who were not, and duration of mechanical support does not seem to have an adverse impact on mortality after cardiac transplantation (19). Most of the patients bridged with an LVAD are, in fact, the more ideal candidates, as they are functionally much better and, in general, have better organ function and pulmonary artery pressure at the time of transplantation.

Given the progress achieved in VAD outcomes demonstrated in controlled clinical trials, it seems obsolete to make the preimplant determination of whether VAD for a given patient is as bridge to transplant, recovery, or destination and is much more prudent to establish that a patient is in need of mechanical circulatory support, regardless of age or overall comorbidities, and leave the question to be resolved by both the patient and the clinicians at a later point in time of support. We anticipate that the future direction is to abandon rigid categories before the implantation and to make the decision on mechanical circulatory support based on: 1) presence of indications; and 2) absence of contraindications.

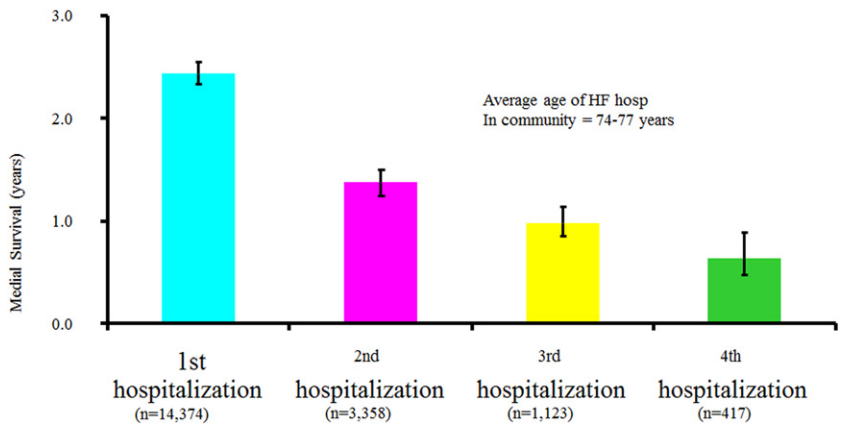

Figure 3 **Median Survival Decreases Progressively After Each Hospitalization for HF**

Hospital admissions not only decrease quality of life, but they are also associated with shorter longevity. Data from Stehlik et al. (10). HF = heart failure.

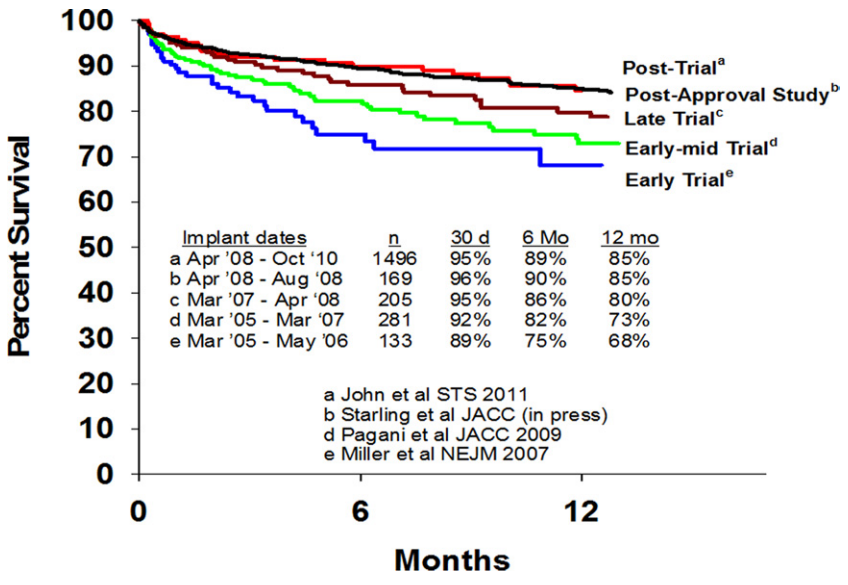

Figure 4 Post-Trial Versus Trial Survival With Continuous Flow LVAD

In this case, real life appears to be better than the trial. Data from John et al. (14). LVAD = left ventricular assist device.

General Criteria for Patient Selection for Mechanical Circulatory Support

Indications for mechanical circulatory support are generally derived from inclusion criteria of clinical trials (Table 1). It is indicated for patients who have symptomatic advanced HF refractory to conventional therapy, including those who become inotrope dependent with significantly impaired cardiac function, with left ventricular ejection fraction typically below 25%. In ambulatory patients, functional status is severely compromised by HF. The most widely used criteria for proving a cardiac cause of HF and candidacy for mechanical circulatory support or transplantation is peak oxygen consumption (Vo_2) of <14 ml/kg/min or <50% predicted for age, sex, and body surface area on cardiopulmonary stress test results. Although there are no specific hemodynamic criteria for device implantation, a cardiac

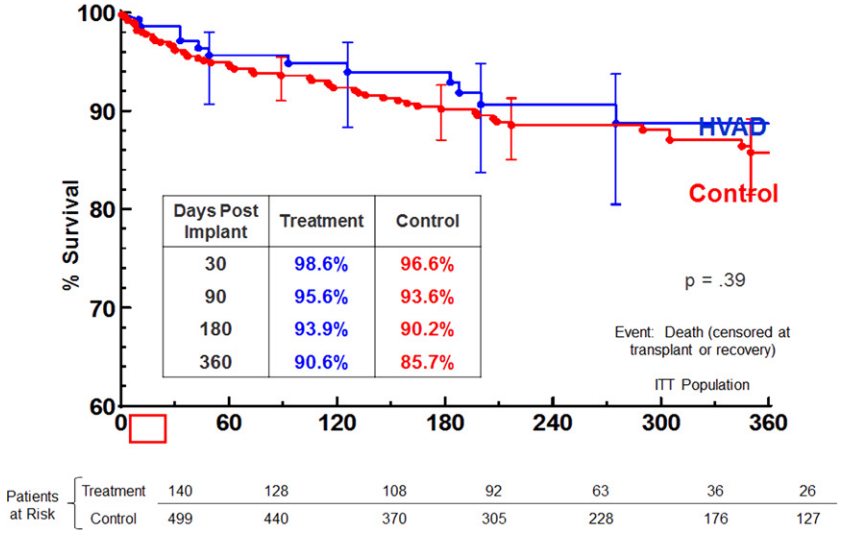

Figure 5 Survival With Heartware Intrapericardial Device

Results from the ADVANCE trial (82).

Table 1 Criteria for Inclusion Into Destination Therapy Clinical Trials

Trial	REMATCH, 2001 (11)	HeartMate II, 2009 (12)
Clinical scenario	1. NYHA class IV for at least 90 days despite best medical therapy or	1. NYHA class IIIB or IV for at least 45 days despite best medical therapy or for the 60 days before enrollment or
	2. Inotrope dependence	2. Intra-aortic balloon pump for 7 days or
		3. Inotrope dependence for at least 14 days before enrollment.
LVEF	<25%	<25%
Peak oxygen consumption	≤12 ml/kg/min	≤14 ml/kg/min or <50% predicted

LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

index <2 l/min/m^2 despite inotropic agents should prompt consideration of mechanical pump placement. Worsening hemodynamics or increasing inotropic requirements or need for use of vasopressors to maintain systemic blood pressure may be more important than the absolute numbers, and following strict hemodynamic criteria should not delay the decision to use VADs. There are several categories of patients developing such profound hemodynamic compromise. Most of the information about them has been derived from the INTERMACS (20).

In 2009, 80% of patients received LVAD as bridge to transplant, 15% as destination therapy, and 5% recovered with subsequent VAD explantation. According to the INTERMACS classification (Table 2), despite published case series and results of risk score stratification showing the worst outcomes in the sickest patients, 80% of patients were in the two most critical levels 1 and 2, with 42% and 38%, respectively. Only 8% of patients were stable on inotropic therapy, and only 12% were free of inotropic support (21). Patients with a profile of 1 or 2 have been shown to have not only inferior survival but also much greater lengths of stay (42 vs. 16 days) than patients who are less acutely sick (22). Patients with cardiogenic shock such as postcardiotomy, acute myocardial infarction, acute myocarditis, or cardiac arrest (INTERMACS level 1 "crash and burn") who currently have the highest mortality (over 60% even with percutaneous or surgical revascularization) (23), may benefit from short-term circulatory support rather than from long-term LVAD. Several types of short-term devices are currently available (24–26). Fortunately, there has been some reduction in the severity of HF and overall comorbidities of patients now being selected for mechanical circulatory support, as confirmed in recent reports from the INTERMACS, particularly for indication for destination therapy (17).

Table 2 INTERMACS Patient Profiles (20)

Level	Definition	Description
1	Critical cardiogenic shock	"Crash and burn"
2	Progressive decline	"Sliding fast"
3	Stable but inotrope dependent	Stable but dependent
4	Recurrent advanced HF	"Frequent flyer"
5	Exertion intolerant	"Housebound"
6	Exertion limited	"Walking wounded"
7	Advanced NYHA class III	Advanced NYHA class III

HF = heart failure; NYHA = New York Heart Association.

Specific criteria for candidate selection for long-term mechanical support. It is generally agreed that patients considered for long-term circulatory support should fulfill the clinical, functional, and hemodynamic criteria for transplant recipient selection. Patients with advanced systolic HF, severely reduced left ventricular systolic function, functional limitations caused by HF, and frequent hospital admissions related to HF are appropriate candidates. However, the indications can be expanded, as reflected in the following sections. Many limitations that would preclude a potential transplant recipient from getting the donor organ can be lifted because no donor heart is needed. Unlike the case of heart transplantation, when the physician must apply ethical considerations and answer the question of the appropriateness of the organ allocation, the decision process for VAD implantation is more medical and social. Additionally, the severity of pulmonary hypertension, which would be prohibitive for cardiac transplantation, is not a contraindication for the VAD.

Absolute contraindications include systemic illness with a life expectancy of less than 2 years or malignancy within 5 years, irreversible renal or hepatic dysfunction, severe obstructive pulmonary disease, or other systemic disease with multiorgan involvement (27). However, LVAD may be an acceptable option for a patient with recent cancer, which might theoretically be cured but who is unable to survive the 5-year disease-free interval typically required for heart transplantation. Similarly, active infection with human immunodeficiency virus or advanced end-organ function such as a serum creatinine concentration of 3.0 mg/dl may not preclude patients from LVAD implantation (28). The overall evaluation process is summarized in Figure 6.

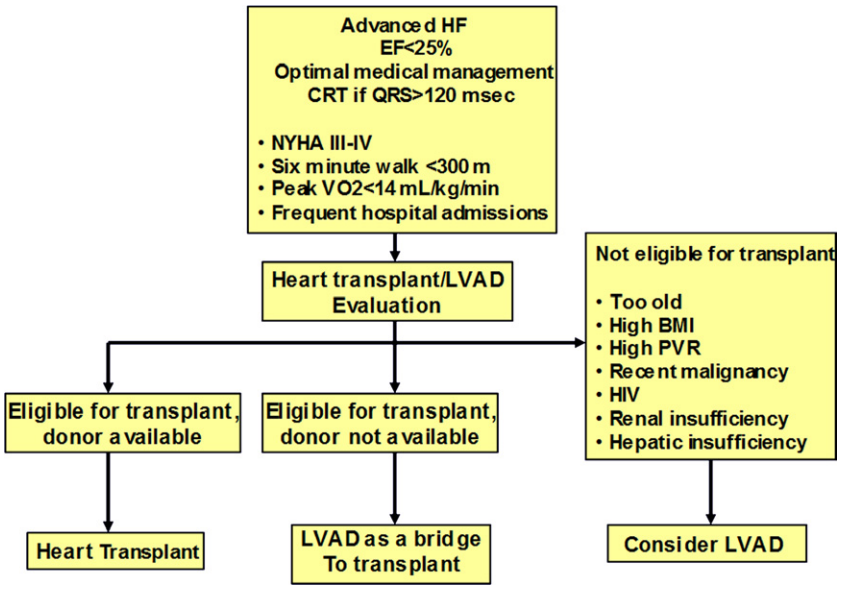

Figure 6 Algorithm for Selection of LVAD Candidates

Risk Scores

Over time, a large number of variables have been identified, largely by univariate analysis, to be associated with increased mortality in patients with HF. However, no one variable can be used to select candidates for mechanical circulatory support. As mechanical pumps become more and more acceptable for less sick HF patients, it is important to consider not only hemodynamic instability but also other features of HF, which limit longevity and compromise quality of life. Several composite risk scores have been developed, which can help stratify patients and predict survival for outpatients, such as the Seattle Heart Failure Risk Score and the Heart Failure Survival Score mentioned earlier. Both score systems have limitations but have been shown to give fairly reasonable estimates of 1-year survival. The Seattle Heart Failure Model, although developed with less sick HF patients, appears to be working better than other scores for mortality prediction before and after VAD implantation (29). Some authors advocate using this score as a virtual control group, predicting the "would be" outcomes if patients were treated medically. The model was also able to predict shorter duration of hospital stay and more favorable hospital course in LVAD recipients (30). The Seattle Heart Failure Model has been selected for use in the REVIVE-IT (Randomized Evaluation of VAD InterVEntion before Inotropic Therapy) trial, and one of the stated goals of that study was to improve risk stratification by adding variables not included in these two models, such as the number of hospitalization for HF and renal function.

More recently, a risk score has been developed to assess perioperative risk of dying prior to hospital discharge after LVAD implantation. This Lietz-Miller score was developed from a large registry of destination therapy patients who received implants of a pulsatile device after U.S. Food and Drug Administration (FDA) approval for commercial use. Use of this score was able to identify those who are at a relatively low risk versus those with a prohibitive risk of dying based on standard laboratory and clinical variables. The major new observations from that study were to point out the importance of nutritional status before a major surgical procedure in patients with advanced HF and the added risk of patients with platelet counts below 148,000 or internation normalized ratio >1.2. The score was validated with a small follow-up study but did not perform as well in a series of over 600 patients who underwent use of continuous flow pumps as bridge to transplantation (31).

Pulmonary Hypertension

From a hemodynamic standpoint, the most serious contraindication for cardiac transplantation is severe fixed pulmonary hypertension, defined as pulmonary artery systolic pressure >60 mm Hg, mean transpulmonary gradient >15 mm Hg, or pulmonary vascular resistance >6 Wood units, which are unresponsive to treatment with various agents alone or in combination. These criteria are correlated with a very high risk for transplantation because of the high likelihood of right ventricular (RV) failure after surgery, which is the second leading cause of death in the first month after transplant. However, pulmonary hypertension is not a contraindication to LVAD placement unless there is severe RV failure pre-LVAD, especially if caused by nonischemic or idiopathic cardiomyopathy. It appears that LVAD place-

ment represents the best tool for reversal of "fixed" or unresponsive pulmonary hypertension. The complete LV unloading achieved by LVAD support cannot be matched by any medical therapy, and often pulmonary pressure and pulmonary vascular resistance normalize after a variable period of time, often as short as 2 to 3 months. The process may be facilitated by use of sildenafil (32).

Right Ventricular Failure

RV failure after LVAD is associated with higher mortality, greater risk of bleeding and/or reoperation, longer hospitalizations, and a higher rate of renal insufficiency (33–35). As noted above, absolute pulmonary pressure or resistance are not important criteria for selection of a patient for an LVAD, but the presence of RV failure pre-LVAD as defined by right atrial pressure of other sophisticated measurements such as tricuspid annular plane systolic excursion (TAPSE) or RV stroke work index. Most patients in cardiogenic shock or advanced HF refractory to medical therapy evaluated for mechanical circulatory support can be managed with only left ventricular support, LVAD. However, the risk of RV failure after LVAD occurs in up to 20% of patients, especially those with nonischemic causes where both ventricles are often equally impaired. In some cases, biventricular support is indicated. In general, LV unloading is beneficial for RV (36). However, in the early postimplantation period, acute increase in venous return and changing LV geometry can compromise the RV. The rate of post-LVAD RV failure decreased compared with early experience but is still substantial at 5% to 13% (34,35).

It is remarkable that unlike in heart transplantation, pulmonary hypertension and high pulmonary vascular resistance do not predict post-LVAD RV failure. To the contrary, lower pulmonary arterial pressure, reflecting poor RV contractility, is a documented risk factor.

Multiple attempts have been made to predict RV failure before LVAD implantation in order to plan biventricular support when needed. Several studies identified multiple risk factors for postimplantation RV failure (33,37–44), and more than half of the risk factors are related to RV dysfunction, such as renal and hepatic insufficiency secondary to congestion, elevated pressure in the right atrium decreased RV stroke work index, and decreased RV contractility by echocardiography (Table 3).

In a small group of patients, Deswarte et al. (45) reported that an increase in TAPSE by 40% and/or an increase in pulmonary artery systolic pressure over 30% with low-dose dobutamine infusion ruled out post-LVAD RV failure with 100% specificity and sensitivity. It appears, therefore, that the clinical syndrome of RV dysfunction before the implant is the most powerful predictor of RV failure after LVAD implantation.

Renal and Hepatic Dysfunction

Many patients with advanced HF have mild to moderate abnormalities of renal function. The serum creatinine concentration may often exceed 2 mg/dl and creatinine clearance below 50 ml/min, which both have been shown to adversely impact survival after transplantation (46). While renal dysfunction related to systemic congestion or impaired renal perfusion secondary to HF may improve with diuresis or inotropic agents, underlying intrinsic renal disease may represent significant comorbidity. If cardiac insufficiency is the primary cause of renal dysfunction it improves after the LVAD implant or transplant (47,48). In patients with baseline glomerular filtration rate of 41.7 ± 11.5 ml/min, it increased to 62.7 ± 25.0 ml/min after 6 months of LVAD support (49).

If intrinsic renal disease is suspected, patients should undergo further workup with 24-h urine collection for protein excretion and creatinine clearance, renal ultrasonography for kidney size, and possibly evaluation of the renovascular system. Standard urinalysis will exclude most parenchymal diseases. Although some centers consider severe renal impairment with glomerular filtration rate <30 ml/min a relative contraindication to LVAD, this approach may be too conservative and result in exclusion of many candidates with high potential to recover. Being on chronic hemodialysis remains a contraindication for long-term VADs as there are few if any dialysis centers that accept patients with an LVAD. Besides, risk of infection is already increased in LVAD patients, and the necessity to establish and maintain dialysis access further increases the danger. Peritoneal dialysis might be safer (50); however most programs will not consider implanting a long-term pump into a patient whose renal function is so profoundly compromised that chronic dialysis is needed.

Transaminase levels more than twice their normal value with or without elevated bilirubin, and associated coagulation abnormalities may reflect right HF or passive congestion; however, primary liver disease, in particular cirrhosis, needs to be excluded, which sometimes requires a liver biopsy.

Bleeding risk. Bleeding has been one of the most common complications since the introduction of LVAD therapy, with a 4-fold increased risk of reoperation for bleeding over standard open heart surgery (51). This is caused by multiple factors including abnormal coagulation at time of surgery, often because of preoperative use of warfarin and/or antiplatelet agents or hepatic congestion, poor nutrition, high venous pressures, and adhesions frequently occurring in patients with previous sternotomy. There is now an important second phase of the risk of bleeding that develops beginning 1 month after implant, which may occur in up to 25% of patients. Increasing age seems to be most correlated with increased risk of bleeding. The most common site of bleeding is in the upper gastrointestinal tract (52–54) and is typically caused by or associated with development of

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Table 3 Risk Factors for RV Failure After LVAD Implantation

Fisrt Author, Year (Ref. #)	n	No. of RV Failures (%)	Risk Factors for Post-VAD RV Failure: Factors Related to Pre-Operative RV Dysfunction	Risk Factors for Post-VAD RV Failure: Factors Unrelated to Pre-Operative RV Dysfunction
Pulsatile LVADs				
Kormos et al., 1996 (78) Novacor	40	17 (42.5)	1. Greater need for inotropic agents 2. Lower RVEF/inotropic need ratio 3. None of the patients with RVEF >20% developed RV failure 4. Higher creatinine	1. Lower mixed venous oxygen saturation 2. Pulmonary edema 3. Poor mental status 4. Fever without infection
Fukamachi et al., 1999 (38) HeartMate I	100		1. Lower pre-operative mean pulmonary arterial pressure 2. Lower RV stroke work index 3. Elevated aspartate aminotransferase	1. Younger age 2. Female 3. Smaller patients 4. Myocarditis
Kavarana et al. 2002 (39) HeartMate I	69	21 (30.4)	1. Higher bilirubin 2. Trend toward lower preoperative RV stroke work index	1. Intra-operative bleeding
Ochiai et al., 2002 (40) 189 HeartMate I (77%) and 56 Novacor (23%)	245		1. Non-ischemic cause 2. Preoperative circulatory support 3. Low mean and diastolic pulmonary arterial pressure 4. Low RV stroke work 5. Low RV stroke work index	1. Female 2. Small body surface area
Dang et al., 2006 (33) HeartMate I	108	42 (38.9)	1. Elevated intra-operative central venous pressure 2. Intra-operative lower systolic and mean blood pressure 3. Lower intra-operative pulmonary arterial pressure	1. Female
Santambrogio, et al., 2006 (44) Novacor	48	8 (16)	1. Higher aspartate aminotransferase 2. Higher alanine aminotransferase. Higher blood urea nitrogen 3. Higher blood urea nitrogen 4. Higher creatinine 5. Lower pulmonary arterial pressure	1. Pre-operative mechanical ventilation
Pulsatile and continuous flow LVADs				
Matthews et al., 2008 (42) Mixed devices	197	68 (35)	1. Vasopressor requirement (OR: 4.8) 2. Aspartate aminotransferase ≥80 IU/l (OR: 3.2) 3. Bilirubin ≥2.0 mg/dl 4. Creatinine ≥2.3 mg/dl (OR: 5.56) 5. Need for hemodialysis (OR: 9.9) 6. Severe RV systolic dysfunction (OR: 2.2) 7. Blood urea nitrogen ≥48 mg/dl (OR: 2.1) 8. Bilirubin ≥2.0 mg/dl (OR: 3.6) 9. Pulmonary artery systolic pressure <50 mm Hg 10. RV stroke work index <450 mm Hg × ml/m^2 (OR: 2.3) 11. Severe tricuspid regurgitation (OR: 1.3)	1. Cardiac arrest preoperatively (OR: 2) 2. Smaller body surface area 3. History of cerebrovascular accident 4. Need for ventilatory support (OR: 3.2) 5. Temporary mechanical LV bridge before LVAD (OR: 3) 6. Absence of a prior sternotomy 7. Intravenous anti-arrhythmic agents (OR: 2.6) 8. White blood cells ≥12.2 k/mm^3 (OR: 2.71) 9. Platelet count ≤ 120 k/mm^3 (OR: 3.4) 10. Albumin ≤ 3.0 g/dl (OR: 1.9)
Fitzpatrick et al., 2008 (79) Mixed devices	266		1. Severe RV dysfunction. (OR: 5.0) 2. Low RV stroke work index RV stroke work index <0.25 mm Hg × l/m^2 (OR: 5.1) 3. Higher central venous pressure 4. Lower pulmonary arterial pressure 5. Creatinine >1.9 mg/dl (OR: 4.8)	1. Mechanical ventilation 2. Previous cardiac surgery (OR: 4.5) 3. Cardiac index <2.2 l/min/m^2 (OR: 5.7) 4. Intra-aortic balloon pump 5. Pre-operative circulatory support 6. Female 7. Smaller body surface area 8. Systolic blood pressure <96 mm Hg (OR: 2.9) 9. Lower mixed venous saturation

Continued on the next page

Table 3 Continued

First Author, Year (Ref. #)	n	No. of RV Failures (%)	Risk Factors for Post-VAD RV Failure: Factors Related to Pre-Operative RV Dysfunction	Risk Factors for Post-VAD RV Failure: Factors Unrelated to Pre-Operative RV Dysfunction
Dracos et al., 2010 (37) Mixed Thoratec and Novacor devices	175		1. Higher bilirubin 2. Higher right atrial pressure	1. Pre-operative intra-aortic balloon counterpulsation (OR: 3.9) 2. Pre-operative intubation 3. Lower platelets 4. Lower cholesterol 5. Smaller left ventricular size 6. Increased pulmonary vascular resistance: 2. 8–4.2 Wood units (OR: 3.0) >4.3 Wood units (OR: 4.1) 7. Destination therapy (OR: 3.3)
Continuous flow LVADs				
Kormos et al., 2010 (80) HeartMate II	484	65 (13)	1.Central venous pressure >15 mm Hg (OR: 2.1) 2. Central venous pressure/pulmonary capillary wedge pressure >0.63 (OR: 2.5) 3. RV stroke work index <300 (OR: 2.9) 4. Blood urea nitrogen >39 mg/dl (OR: 1.7) 5. Aspartate aminotransferase >49 mg/dl (OR: 1.7)	1. Ventilatory support (OR: 5.7) 2. Hematocrit ≤ 31% OR (2.3) 3. More blood transfusions 4. White blood cells >10.4 × 10^3/ml (OR: 2.2)
Baumwol et al., 2011 (81) Heartware	40	13 (32.5)	1. More severe tricuspid regurgitation	

LVAD = left ventricular assist device; OR = odds ratio; RV = right ventricle; VAD = ventricular assist device.

arterial-venous malformations, primarily located in the stomach or early portions of the small bowel. This seems to be a unique sequela of continuous flow physiology, as it was not seen with the first generation of pulsatile flow devices. Patients with prior history of gastrointestinal bleeding should have upper and lower endoscopy before LVAD. Recent attention has been directed at the uniform reduction in multimers of von Willebrand factor in the serum in response to nonpulsatile flow as one possible explanation for the increased bleeding associated with continuous flow VADs (55,56). Presence of bleeding diathesis may be a serious contraindication to LVAD unless coagulopathy is caused by reversible hepatic dysfunction. Low platelet count before implantation also predicts poor outcomes. Sometimes, presence of heparin-induced thrombocytopenia antibody needs to be excluded.

Patient Size Considerations

Implantation of LVADs was previously restricted to patients with a body surface area >1.5 m^2, but the continuous flow LVADs, which are one-seventh the size of pulsatile devices, have been shown to be safely used in patients as low as 1.3 m^2 (12), which has allowed these nonpulsatile VADS to be used in a significantly higher percentage of women and smaller adults and adolescents. The Heartware LVAD, which is implanted intrapericardially, practically does not have body size limitations. This is in contrast to heart transplantation where most programs limit donors to ± 15% of the weight of the recipient.

There are many groups that have been underserved by LVAD therapy including women, due primarily to the large size of the first-generation pulsatile LVADs. The percentage of women in recent LVAD trials of the much smaller continuous flow pumps has increased from 8% to 25%, with comparable results to males.

Obesity. There are conflicting data about the influence of obesity on transplant outcomes. Obesity may be associated with increased morbidity, complications such as infection, and poor perioperative survival and difficulty identifying an appropriately sized donor heart. The 5-year mortality can double in obese patients compared with normal-weight patients (57,58). In many centers, body mass index >35 kg/m^2 is a relative contraindication for cardiac transplantation. Such patients are encouraged to lose weight before listing. On the other hand, the same degree of obesity may not be a contraindication to LVAD implantation. One-year survival of morbidly obese HF patients who receive LVAD as destination treatment was not different from patients with normal weight (59). In a recent report, although infections occur more frequently in the overweight, primarily because of drivelines, which rest within skin folds (60). In some cases, patients with LVAD manage to lose so much weight that they became acceptable candidates and were successfully transplanted (61). There is increasing interest in before or after LVAD bariatric surgery to improve weight loss and reduce potential complications. Overall, it appears that at least mid-term outcomes are comparable across the whole spectrum of body mass index (62).

Cachexia. The patient with cardiac cachexia marked by poor nutrition status and low albumin and total protein concentrations (<3.5 mg/dl and 6 mg/dl, respectively) is at a high risk for postoperative death as well as complications, infection, and poor wound healing. Prealbumin and total

cholesterol are even more sensitive markers of nutritional status and should be evaluated in all candidates for LVAD therapy. Nutritional issues have to be addressed before the implant to optimize outcomes (63).

Age. One of the most controversial issues in the field of patient selection for advanced HF is age. Many transplant programs are reluctant to list "elderly" candidates. The cutoff age varies but is typically between 65 and 71 years of age. In contrast, there is no absolute age cutoff for LVADs, and older patients may have easier access to mechanical pumps than to donor organs. While some authors are relatively pessimistic, reporting low 1-year survival in patients over 65 years of age (64), others report excellent outcomes. In a study of 30 patients over 70 years of age, Adamson et al. (65) demonstrated survival and length of stay that were no different from that in younger patients, with good functional recovery and quality of life. Thus, age should no longer be considered a limitation to LVAD therapy, but older patients should be more closely evaluated for potential age-related diseases, such as malignancy. Some geriatric scores like fragility indices (66) might be helpful for additional stratification of elderly candidates.

Psychosocial evaluation. Like current recommendations for transplantation, all VAD candidates should undergo evaluation by a trained mental health professional and social workers in order to ensure that they are able to receive adequate postoperative care and medications before the decision is made to proceed with the surgery. Psychosocial criteria that may predict a poor postoperative outcome include previous noncompliance, chemical dependencies (alcohol and drugs), lack of an adequate support system, personality disorder, underlying mental illness, organic brain disorders, or mental retardation. Intellectual function is a difficult assessment in these patients, who often have very reduced cardiac output pre-LVAD and may demonstrate improved cognitive function post-LVAD. Most programs include some type of intellectual testing before accepting a patient for LVAD placement to minimize the risk of catastrophic problems such as removing both batteries at one time or not recognizing alarms on the device controller.

Structural Cardiac Diseases

Severe aortic regurgitation needs to be corrected simultaneously with LVAD placement to avoid a "closed loop" circulation between LV and ascending aorta. In most cases, a bioprosthetic valve is placed; sometimes aortic valve is completely closed surgically, which makes the patient very sensitive to any LVAD malfunction because they become totally dependent on the mechanical pump (67). Mitral valve surgery is necessary only in the presence of significant mitral stenosis compromising LV filling. Intracardiac shunts are typically closed at the time of VAD implantation. Pre-existing mechanical or biological prosthetic valves, mitral or aortic, usually do not cause complications during LVAD implantation (68,69). It may be worth mentioning that in case of aortic valve insufficiency already in the presence of LVAD, transcatheter aortic valve replacement is a possibility (70). The growing population of adult patients with congenital heart disease with RV failure is another pool of potential candidates for VADs (71).

Infection

Active infection is a contraindication to VADs. Patients with such infection should be aggressively treated in collaboration with infectious diseases specialists. Bacterial infections are especially dangerous because if the VAD is seeded, it is almost impossible to sterilize with antibiotics. On the other hand, controlled viral infections such as human immunodeficiency virus infection may not be a contraindication to VADs (72).

Moving to Patients With Less Severe Heart Failure

There is now a clear and rapidly escalating trend nationally for patients to undergo LVAD implantation as a totally elective operation, with an increasing percentage being admitted from home for a scheduled surgery. This approach has multiple advantages including reduced nosocomial infection, generally better condition of the patient, having been at home rather than in an intensive care unit for rest and nutrition, and overall functional capacity. Boyle et al. (22) demonstrated that patients with a less severe INTERMACS grade of HF at the time of LVAD implantation have not only better survival but also significantly shorter hospital lengths of stay than those with more severe HF or shock at the time of implantation. Most importantly, there is a clear trend to offer mechanical circulatory support to less-severe HF patients.

Until recently, mechanical circulatory support was reserved for patients with profound shock and refractory HF. However, the number of implantations is rapidly growing. The very good outcomes now reported in several clinical trials with continuous flow LVADs in nonshock patients (7,12,73,74) has led to equipoise about the presumed equality of outcomes with the use LVADs versus standard medical therapy as a therapeutic option for patients with less severe HF. Following recommendations of an expert panel, the National Heart, Lung, and Blood Institute has initiated the Randomized Evaluation of VAD InterVEntion before Inotropic Therapy study, which is a randomized trial comparing LVAD to optimal medical therapy. This trial will hopefully more clearly define the risk factors association with mortality in today's management of HF. The expected survival in the LVAD cohort is predicted to be 75% to 80% at 1 year and 70% at 2 years. If this trial proves that LVAD therapy can provide not only superior survival, but also significantly

better functional improvement and quality of life, it will lead to the largest increase in LVAD therapy ever. The MEDAMACS (Medical Arm of Mechanically Assisted Circulatory Support) pilot screening trial will also shed some light on the outcomes in patients with advanced HF and help identify the next group of candidates who will likely benefit from earlier VAD implantation.

Impact of New Devices

Development of new devices can once again change dramatically the whole process of patient selection, shifting it toward more stable and benign and less advanced stages of the disease. Additionally, smaller and simpler devices may reduce surgical complications and lower the threshold for referral of patients for VADs. Recent recommendation of the FDA advisory panel to approve centrifugal HeartWare has paved the road to its approval for commercial use in the near future. Smaller size and intrapericardial location may help adoption of this pump, provided that clinical outcomes are not inferior to the currently used HeartMate II.

Another model being tested is a miniaturized LVAD requiring only minimal surgery, which will potentially expand indications to earlier stages of HF and increase the market of candidates. It is implanted through the left ventricular apex with a distal cannula in the ascending aorta. This LVAD does not require sternotomy, device pocket, cardiopulmonary bypass, ventricular coring, and construction of an outflow graft anastomosis (75).

Another concept that can potentially revolutionize the approach to VAD candidate selection is partial circulation support. The Synergy Pocket micro-pump device (CircuLite, Inc., Saddle Brook, New Jersey) has the inflow cannula in the left atrium and the outflow in the right subclavian artery. It provides blood flow of 3 l/min. It has already demonstrated significant and steady improvement of many hemodynamic parameters (76,77). This device is implanted off pump via a mini-thoracotomy and placed like a pacemaker in a right subclavicular subcutaneous pocket (like a pacemaker).

However, the real change in selection of a patient for LVAD or heart transplant will occur when eventually the problem of transcutaneous energy supply is solved and the "Achilles heel" of all currently available devices, namely the driveline going through the skin and posing continuous risk for infection, disappears.

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