Should Left Ventricular Assist Device Be Standard of Care for Patients With Refractory Heart Failure Who Are Not Transplantation Candidates?

Left Ventricular Assist Devices Should Not Be Standard of Care for Transplantation-Ineligible Patients

Anjali Tiku Owens, MD; Mariell Jessup, MD

At 40 years of age, the lifetime risk of developing heart failure (HF) is 1 in 5 for men and women in the United States. Approximately half of patients who are ultimately diagnosed with HF will die within 5 years; the associated morbidity, hospitalization rate, and loss of functional capacity are more difficult to calculate. Among the 5 million American patients currently living with HF, it is estimated that 200 000 patients have American College of Cardiology/American Heart Association stage D or refractory HF, resulting in markedly diminished functional status and survival.1,2 In 2012, 2 therapies are available to potentially prolong survival and to improve quality of life for end-stage HF patients: heart transplantation and long-term mechanical circulatory support in the form of a ventricular assist device (VAD). For permanent mechanical support, also referred to as destination therapy (DT), the Food and Drug Administration approved the use of the HeartMate II (Thoratec Corp, Pleasanton, CA) left ventricular assist device (LVAD) in January 2010. This device supports only the left ventricle; no biventricular device is approved for long-term therapy at this time.

Response by Mehra and Domanski on p 3094

Many advanced HF patients are not appropriate candidates for transplantation or permanent LVAD because of comorbid conditions or age. After excluding these patients, clinicians must critically evaluate individual patient eligibility for transplantation or VAD. The indications for and complications expected after each procedure are increasingly recognized as distinct; the skills needed by clinicians who must care for these 2 types of patients are garnered in 2 complementary but separate experiential care settings. The therapies are neither equivalent in historical experience and outcomes nor interchangeable. Transplantation has been available for decades, with well-documented selection criteria, management protocols, and outcomes. As we begin to understand how to appropriately use VADs as a therapeutic option in patients with advanced HF, it has become apparent that many patient characteristics leading to ineligibility for transplantation also preclude or negatively influence outcome after VAD. There are undeveloped patient selection criteria, unacceptably high rates of complications, and insufficient long-term survival data with permanent VADs to warrant designation as second-line therapy to all transplantation-ineligible patients.

Furthermore, what goal would be achieved by mandating permanent VAD as standard of care for transplantation-ineligible patients: to attempt to salvage survival for all end-stage HF patients? Is survival our only standard in the absence of enhanced quality of life? Currently, we lack
patient-reported outcomes with respect to quality of life after LVAD, and as a nation, we spend ≈16% of our gross domestic product on health care, without including the potential widespread dissemination of this costly therapy. To suggest that all patients ineligible for transplantation should receive a VAD is equivalent to mandating that all persons ineligible for an automobile driver’s license be licensed to pilot a jet. It is our opinion that to designate permanent ineligibility for medical therapy (LVEF < 20%; peak VO₂ < 12 mL·kg⁻¹·min⁻¹) or mechanical circulatory support with an intra-aortic balloon pump counterpulsation device or VAD

Absolute contraindications
- Systemic illness with a life expectancy < 2 y despite heart transplantation, including:
  - Active or recent solid-organ or blood malignancy within 5 y
  - AIDS with frequent opportunistic infections
  - Systemic lupus erythematosus, sarcoid, or amyloid with active multisystem involvement
  - Irreversible renal or hepatic dysfunction in patients considered for only heart transplantation
  - Significant obstructive pulmonary disease (FEV₁ < 1 L/min)
- Fixed pulmonary hypertension
  - Pulmonary artery systolic pressure > 60 mm Hg
  - Mean pulmonary gradient > 15 mm Hg
  - Pulmonary vascular resistance > 6 Wood units

Relative contraindications
- Age > 70 y
- Any active infection (with exception of device-related infection in VAD recipients)
- Active peptic ulcer disease
- Severe diabetes mellitus with end-organ damage (neuropathy, nephropathy, or retinopathy)
- Peripheral vascular disease not amenable to surgical or percutaneous therapy
- Morbid obesity (body mass index > 35 kg/m²) or cachexia (body mass index < 18 kg/m²)
- Creatinine > 2.5 mg/dL or creatinine clearance < 25 mL/min
- Bilirubin > 2.5 mg/dL, serum transaminases > 3×, INR > 1.5 off warfarin
- Severe pulmonary dysfunction with FEV₁ < 40% normal
- Recent pulmonary infarction within 6 to 8 wk
- Difficult-to-control hypertension
- Irreversible neurological or neuromuscular disorder
- Active mental illness or psychosocial instability
- Drug, tobacco, or alcohol abuse within 6 mo
- Heparin-induced thrombocytopenia within 100 d

AIDS indicates acquired immunodeficiency syndrome; INR, international normalized ratio; and VAD, ventricular assist device.

*May be suitable for heart transplant if inotropic support and hemodynamic management produce a creatinine < 2 mg/dL and creatinine clearance > 50 mL/min. Transplantation may also be advisable as combined heart-kidney transplantation.

Adapted from Mancini and Lietz.

Transplantation Is Well-Studied With Defined Risks, Outcomes, and Processes of Care

The first human-to-human heart transplantation occurred in 1967: ≈2200 heart transplantations are performed each year in the United States, a number that has remained relatively stable over the years because of a limited supply of donor organs. Moreover, cardiac transplantation is a procedure that has gained wide acceptance and is undertaken in many countries throughout the world. Thus, a host of scientists and clinicians have had >4 decades to clearly delineate the pros and cons of the operation and the immunosuppression that follows. First, consider the well-described indications for heart transplantation, a list that has remained virtually unchanged. A thorough review of transplantation was published in 2010 by Mancini and Lietz, which has been preceded by many others. Tables 1 and 2 outline indications and contraindications, respectively, for heart transplantation as adapted from these reviews and guidelines. Importantly, many patients with severe HF are ineligible for cardiac transplantation. This necessitates a different therapeutic approach for these patients; a permanent VAD is one of several options.

The surgical procedure for transplantation has been refined and perfected over the last several decades, resulting in well-defined risks and low mortality in expert hands. Pretransplantation care and posttransplantation care have been thoroughly studied, and guidelines and consensus processes of care exist. There have been some meaningful changes to patient selection criteria over the years, with older patients, diabetics, and patients with renal dysfunction receiving transplantations today who would not have been eligible 20 years ago. Nevertheless, we continue to refine risk prediction for outcome after transplantation with a new prediction model, eg, the Index for Mortality Prediction After Cardiac Transplantation (IMPACT) score, published recently. Outcomes and expected longevity have significantly improved, albeit marginally, in the modern era of immunosuppression and transplantation. However, what has altered the risk-benefit analysis in terms of timing and the choice of transplantation.
is the advent of better medical, device, and surgical therapy for HF, including β-blockers and aldosterone antagonists; device strategies, including implantable cardioverter-defibrillator and cardiac resynchronization therapy; and finally VADs themselves, which have been used successfully in the bridge-to-transplantation population.5

Indeed, the very existence of an alternative to transplantation has ushered in the current era of risk modeling.10,11 Before VADs, failing patients either were deemed transplantation candidates (infrequently) or were managed through their inevitable demise. Contrast that to the current decision making surrounding a 67-year-old patient with systolic HF, significant coronary artery disease with less-than-ideal surgical targets, paroxysmal atrial fibrillation, and New York Heart Association class IIIb symptoms despite angiotensin-converting enzyme inhibitors, β-blockers, aldosterone antagonists, and diuretics: angioplasty or bypass surgery, rate or rhythm control of atrial fibrillation, laboratory-based ablation or surgical ablation at the time of bypass surgery, cardiac resynchronization therapy and/or implantable cardioverter-defibrillator, transplantation, or DT VAD, with an almost endless list of additional questions. It is now standard of care that all of these decisions are made before cardiac transplantation is considered. Transplantation is the last option; donors are a scarce resource.

Permanent LVAD Is a Work in Progress With Significant Morbidity and Mortality

In contrast, the selection criteria for permanent VAD implantation have been codified in the United States primarily by the Centers for Medicare and Medicaid Services. There are varying other opinions on what constitutes an appropriate candidate for permanent VAD10,12–14; published indications and contraindications are reproduced in Table 3, adapted from Khazanie and Rogers14 and others. Surgical techniques for VAD implantation continue to evolve rapidly, in part as a result of the influx of new technologies and pumps.15 Needless to say, there is a significant learning curve associated with implantation, the perioperative care, and the long-term management of each pump. Operative mortality in available clinical trials is significantly higher for VAD implantation than for transplantation. In addition, there are no well-studied, evidence-based guidelines in place for the standardized care of VAD patients. We continue to rely on investigator experience derived primarily from clinical trial data.16 In fact, a recent survey of VAD coordinators from approved DT-designated centers reported little consensus with respect to the management of VAD patients.17 It has been suggested that implementation of standardized, systemic patient care algorithms for VAD patients may improve outcome and minimize complications.18

There continues to be significant morbidity and mortality associated with second- and third-generation VADs. In the short term, perioperative bleeding, sepsis, multiorgan failure, and right ventricular failure result in death or prolonged hospitalization.16,19 The most concerning long-term complications in the DT population are stroke, bleeding, and infection. Neurological complications can be hemorrhagic or ischemic, often complicating the management of anticoagulation and post-VAD recovery.20 Unfortunately, the rate of stroke has not improved with newer second-generation devices.19 Bleeding complications, both neurological and gastrointestinal, stem primarily from anticoagulation, the development of angiodysplasia, and acquired von Willebrand disease secondary to continuous flow.21,22 Infectious complications range from VAD-associated driveline or pump-pocket infection to localized non-VAD infection to overwhelming sepsis.23 In the HeartMate II DT trial, 18% of continuous-flow patients had a stroke, 35% had VAD-related infection, 36% had sepsis, 30% experienced bleeding requiring surgery, ~25% had right HF, 38% had respiratory failure, 16% had renal failure, and a striking 94% were rehospitalized.19 The long-term significance of some device complications such as

### Table 3. Indications and Contraindications for Left Ventricular Assist Device Placement

<table>
<thead>
<tr>
<th>Indications</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>New York Heart Association functional class IV heart failure</td>
<td>Morbid obesity</td>
</tr>
<tr>
<td>Left ventricular ejection fraction &lt;25%</td>
<td>Small body (body surface area &lt;1.5 m²)</td>
</tr>
<tr>
<td>Failure to respond to optimal medical management for at least 45 of the past 60 d</td>
<td>Chronic renal dysfunction but not dialysis dependent</td>
</tr>
<tr>
<td>Intra-aortic balloon pump-dependent for 7 d</td>
<td>Mild to moderate liver dysfunction</td>
</tr>
<tr>
<td>Intravenous inotrope-dependent for 14 d</td>
<td>Malnutrition</td>
</tr>
<tr>
<td>Functional limitation with peak oxygen consumption ≤14 mL·kg⁻¹·min⁻¹</td>
<td>Severe untreated mitral stenosis and aortic regurgitation</td>
</tr>
<tr>
<td>Relative contraindications</td>
<td>Absolute contraindications</td>
</tr>
<tr>
<td>Sepsis or current active infection</td>
<td>Sepsis or current active infection</td>
</tr>
<tr>
<td>Severe right heart failure</td>
<td>Severe right heart failure</td>
</tr>
<tr>
<td>Untreated, severe carotid artery disease</td>
<td>Untreated, severe carotid artery disease</td>
</tr>
<tr>
<td>Severe obstructive/restrictive pulmonary disease</td>
<td>Severe obstructive/restrictive pulmonary disease</td>
</tr>
<tr>
<td>Irreversible severe cerebral injury</td>
<td>Irreversible severe cerebral injury</td>
</tr>
<tr>
<td>Dialysis-dependent renal failure</td>
<td>Dialysis-dependent renal failure</td>
</tr>
<tr>
<td>Elevated international normalized ratio from liver failure or disseminated intravascular coagulation</td>
<td>Any severe end-organ failure</td>
</tr>
<tr>
<td>Heart failure that is expected to recover without mechanical circulatory support</td>
<td>Heart failure that is expected to recover without mechanical circulatory support</td>
</tr>
<tr>
<td>Noncardiac illness likely to limit survival to &lt;2 y</td>
<td>Noncardiac illness likely to limit survival to &lt;2 y</td>
</tr>
</tbody>
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*Reproduced from Khazanie and Rogers14 with permission of the publisher.
aortic valve insufficiency is only now being recognized as we gather a cohort of patients who are several years out from implantation.\textsuperscript{24} Although these complication rates represent improvement compared with pulsatile-flow pumps, they remain high, underscoring the importance of careful patient selection and management protocols. In fact, the primary focus of current clinical investigations is to understand more completely which patients have the best outcome with a VAD compared with their course without one.

Perhaps most important, we still have very few data on long-term (eg, >2 years) survival with the continuous-flow VADs. The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) Third Annual Report\textsuperscript{25} recently noted an increase in 1-year survival from 61\% with pulsatile-flow pumps to 74\% with continuous-flow pumps, with limited additional follow-up. This improvement in 1-year survival is promising and is likely a reflection of not only the newer device technology but also the decreased rate of implantation in sicker patients. The percentage of patients in critical cardiogenic shock (INTERMACS patient profile 1) before implantation has decreased from 35\% to 17\%. In fact, at the time of VAD implantation, the INTERMACS patient profiles were 2 through 4 (progressive decline, stable but inotropic dependent, and recurrent advanced HF, respectively) in >80\% of DT patients. Thus, a patient with cardiogenic shock who is supported on multiple pressors is unlikely to do well with a DT VAD but might have a good outcome with a timely heart transplantation.

### Significant Overlap Exists Between Contraindications for Transplantation and Permanent LVAD

In our experience at a large transplantation center, a noteworthy number of patient characteristics that preclude transplantation will also prohibit VAD or, at the very least, will increase the chance of poor outcome after VAD. Specifically, noncardiac chronic illness that is likely to limit survival, significant obstructive or restrictive lung disease, active infection/sepsis or risk of recurrent infection, coagulopathy, cachexia/malnutrition, psychosocial instability, lack of caregiver support, significant neurocognitive dysfunction, prior stroke, medical noncompliance, alcohol/drug/tobacco abuse, multiple sternotomies, and severe end-organ dysfunction are all factors that lead to poor outcome after transplantation and after permanent VAD. It is worth critically examining the patient characteristics of DT VAD patients from the INTERMACS registry further. Very few patients selected for DT in this registry cohort were deemed ineligible for transplantation owing to one of the high-risk features listed above but rather were excluded from transplantation for obesity, renal dysfunction, and some pulmonary hypertension\textsuperscript{25} (see Table 4). These factors do not generally preclude a good outcome with DT VAD. Except for age, these factors tend to be modifiable, a concept supported by the fact that \textasciitilde10\% of the INTERMACS DT cohort went on to receive heart transplantation.

Critical to the issue of selecting appropriate DT VAD candidates is the subject of resource use. Much has been written over the years about the optimal selection of transplantation candidates because of the scarcity of donor organs. The subtext of this argument is that poor selection leads to the death of the recipient, loss of the donor graft, and a large expenditure of money with an unsatisfactory outcome. The same can be said for the unwise strategy of choosing VAD

\begin{table}
\centering
\caption{Transplantation Contraindications, Adult Primary Implantations: INTERMACS, June 2006–June 2010}
\begin{tabular}{|l|c|}
\hline
Contraindication & \( n \) (%)
\hline
\hline
\textbf{Modifiable} & \\
Renal dysfunction & 86 (22) \\
High body mass index & 62 (16) \\
Pulmonary hypertension & 45 (12) \\
Still smoking & 27 (7) \\
Limited social support & 20 (5) \\
Severe diabetes mellitus & 20 (5) \\
Repeated noncompliance & 16 (4) \\
Illicit drug use & 14 (4) \\
Alcohol abuse & 13 (3) \\
Patient refuses transplantation & 11 (3) \\
Limited cognition/understanding & 8 (2) \\
Contraindication to immunotherapy & 7 (2) \\
Risk of recurrent infection & 5 (1) \\
Severe depression & 4 (1) \\
Current infection & 3 (1) \\
Malnutrition/cachexia & 3 (1) \\
Musculoskeletal limitations & 3 (1) \\
\hline
\textbf{Nonmodifiable} & \\
Advanced age & 128 (33) \\
Other comorbidity & 35 (9) \\
Peripheral vascular disease & 31 (8) \\
Pulmonary disease & 30 (8) \\
Frailty & 20 (5) \\
Fixed pulmonary hypertension & 18 (5) \\
History of solid-organ cancer & 18 (5) \\
History of lymphoma, leukemia & 12 (3) \\
Multiple sternotomies & 12 (3) \\
Other major psychiatric diagnosis & 6 (2) \\
Heparin-induced thrombocytopenia & 5 (1) \\
Major stroke & 5 (1) \\
Allosensitization & 1 (<1) \\
Recent pulmonary embolus & 1 (<1) \\
\hline
\end{tabular}
\end{table}

\textsuperscript{INTERMACS indicates Interagency Registry for Mechanically Assisted Circulatory Support.}

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recipients only on the basis of unsuitability for transplantation rather than their optimal characteristics for a DT VAD. Poor selection leads to death of the recipient and a large expenditure of money, also an increasingly scarce resource.

**There Is End-Stage Heart Disease That Is Not Amenable to a Permanent VAD**

In addition to the patient selection factors listed above, a proportion of patients with complex congenital heart disease, hypertrophic cardiomyopathy, restrictive cardiomyopathy, valvular heart disease, or the presence of mechanical valves may not be eligible for heart transplantation for standard reasons but are also not candidates for VAD because of the nature of their structural heart disease. A much larger proportion of patients have a biventricular cardiomyopathy and are not candidates for permanent LVAD because of severe right heart failure. As we have painfully learned, right heart dysfunction is a major cause of morbidity and mortality after LVAD implantation. Until we have better therapies to treat right HF, better strategies to predict or prevent right HF, or the availability of permanent, ambulatory biventricular support, this will continue to be a major limitation to the use of LVAD as standard of care in transplantation-ineligible patients (see the Figure).

Patients who meet indications for heart transplantation owing to intractable angina or arrhythmias may be too healthy to meet current Centers for Medicare and Medicaid Services criteria for permanent LVAD. The role of permanent LVAD in New York Heart Association functional class III patients may be examined by new trials designed to specifically assess the long-term effect of VADs in less ill patients. It would be premature to extend LVAD therapy to this group until a randomized assessment of risk, benefit, and outcomes is performed. We need to more accurately predict who is sick but not too sick to derive optimum benefit from chronic mechanical support.

**Conclusions**

Over the years, many transplantation clinicians have had the immensely satisfying experience of watching the implantation of a VAD result in the salvage of a dying patient, snatching life from the jaws of death, allowing transplantation to proceed as planned. LVADs were successful in these critical circumstances precisely because they were a temporary solution. Before the advent of VADs, we lost patients at transplantation because they were too sick. We have learned the lesson again: There are some patients who are too sick for DT VAD. Criteria for LVAD for DT implantation are evolving, and we predict that transplantation ineligibility will soon not even be included in the list.

Given the many options available to treat a failing heart, we advocate a collaborative approach to determine optimal patient management. Medical centers without the resources to support a costly VAD or transplantation program should be encouraged to refer patients to a tertiary care center for evaluation. On the other hand, the development of nontransplantation DT VAD centers is a growing trend. In these situations, we believe it is best for the patient to have the opportunity to be evaluated at a center where all options are available. Evaluation can occur in person if feasible for the patient. However, if geography or cost is a limiting factor, regular, multidisciplinary teleconferences between nontransplantation DT VAD centers and tertiary transplanting institutions could be instituted, during which patients can be
discussed for a virtual evaluation. If DT VAD is deemed the best option and appears to be low risk, the nontransplantation VAD center can then perform the implantation. If deemed high risk from an operative perspective or transplantation is the best option, the patient is referred to the tertiary center. Using this model of care, for example, we have found the conference to be a useful forum not only for discussion of therapeutic options for the failing heart but also for ongoing dialog on VAD complications and postoperative, shared care management of VAD patients.

LVADs are an option to treat some forms of stage D HF, just as high-risk bypass surgery, aortic valve replacement, and ventricular tachycardia ablation are other techniques currently available. These very promising devices are expensive and require a complex system of care; their potential to significantly alter the relentless morbidity and mortality associated with end-stage HF seems limitless at the moment. Let us not limit their use to a second-line treatment.

Disclosures
Dr Jessup served as national coprincipal investigator in the Heart-Ware ENDURANCE trial until April 12, 2012, but received no monetary compensation. Dr Owens reports no conflicts.

References
Response to Jessup and Owens

Mandeep R. Mehra, MD; Michael J. Domanski, MD

We appreciate the enthusiasm for left ventricular assist devices (LVADs) expressed by Drs Owens and Jessup that extols the “limitless” potential of these devices and calls on the community to “not limit their use to second-line treatment.” Heart transplantation is not a viable option for the vast majority of patients in late-stage heart failure, and LVAD therapy, in the absence of contraindications, provides superior survival and quality of life compared with optimal medical therapy. The past several decades have seen the painstaking evolution of LVADs from proof of concept to durable therapy with substantial life-extending outcomes. Device technology is rapidly advancing in the arena of an improving biological interface (to decrease shear stress and thrombosis), enhanced durability, and internally contained tether-free systems. In tandem with engineering advances, we are learning to better match patients to devices, as noted by the shift to selection from cardiogenic shock to less sick patients. It is important to understand that we do not suggest a “mandate” for the use of LVADs in “all transplantation-ineligible patients.” We agree with the obvious, as stated by Drs Jessup and Owens, that careful selection of patients for LVAD implantation is needed to ensure a favorable benefit-to-risk ratio. It is important to note that a “standard” denotes the attention, caution, and prudence that a reasonable clinician in the circumstances would exercise. In this regard, we believe that LVAD therapy now extends into the realm of such a “standard of care” for carefully selected patients with refractory heart failure who are otherwise deemed transplantation ineligible.
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