Is Left Ventricular Assist Device Therapy Underutilized in the Treatment of Heart Failure?

Keeping Left Ventricular Assist Device Acceleration on Track

Garrick C. Stewart, MD; Lynne W. Stevenson, MD

Almost 50 years ago, the National Heart, Lung, and Blood Institute launched the journey of mechanical circulatory support. These pioneers have included innovative engineers, cardiac surgeons, and stalwart patients accompanied by devoted families, who together have led us to a horizon where widespread clinical utilization is finally within sight. The pace of progress is always slower than projected. Despite our impatience, we should not rush too far beyond the light of the wagons onto terrain that is less hospitable to medical technological advances than it was 50 years ago. Since the approval of a continuous-flow destination device in January 2010, there has already been a 10-fold increase in the implantation of left ventricular assist devices (LVADs) for lifetime support, the major avenue for expansion of circulatory support. We would join advocates for more systematic evaluation of lifetime ventricular assist device (VAD) therapy in the patients listed with high priority for transplantation (a small population) and ambulatory patients with class IV symptoms (a population of unknown size and comorbidities).

It is our position, however, that the current basis of evidence for selection and management of patients with LVAD does not support more aggressive acceleration of LVAD utilization than is already underway.

Recent History of LVAD Clinical Trials

After decades of painstaking incremental development, recent clinical progress has been rapid, with each device hailed as the breakthrough until overtaken by the next. The pulsatile Novacor (WorldHeart, Inc., Salt Lake City, UT) and Heartmate (Thoratec, Inc., Pleasanton, CA) devices were approved to keep people alive as a bridge to transplant without randomized comparison to medical therapy. The first and only randomized, controlled trial of an implantable circulatory support device compared with medical therapy was instead for lifetime support without transplantation; the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial with the pulsatile Heartmate XVE showed an unprecedented doubling of early survival to 52% at 1 year. Evidence from 22 patients surviving 1 year and 5 patients surviving 2 years led to approval for destination therapy (DT) as lifetime support (Table). The pulsatile Novacor device, which was remarkably reliable, also improved outcomes compared with a nonrandomized cohort of inotrope-dependent patients. However, 1-year survival was only 27%, with a high rate of neurological events, and the device was retired.

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Despite the landmark DT approval in 2003, there was limited LVAD use for DT, which led to concern that cardiologists were unduly reluctant to refer their patients for the approved pulsatile device. The next major DT trial compared the pulsatile XVE with the smaller, quieter, more reliable continuous-flow Heartmate II. This trial compared device with device, rather than device with medical therapy. The new device was tested as DT in a population that was slightly younger and excluded the highest-risk patients as defined by the REMATCH trial. As highlighted by Fang, both DT trials showed similar 50% to 60% survival at 1 year with the XVE device despite nearly a decade of intervening intervention.
inhibitors, if tolerated, for at least 60 of the last 90 days
b. Left ventricular ejection fraction <25%
c. Functional limitation with peak oxygen consumption of <12 mL \( \cdot \) kg\(^{-1} \) \( \cdot \) min\(^{-1} \) or continued need for intravenous inotropic infusions owing to symptomatic hypotension, decreasing renal function, or worsening pulmonary congestion
d. The patients has the appropriate body size (for XVE \( \geq 1.5 \) m\(^2\))

VAD implantation as destination therapy must be performed in a facility approved for this purpose, variably stated since 2003. ACE indicates angiotensin-converting enzyme.

In contrast, the survival with the new continuous-flow device for DT was significantly better, 68% at 1 year and 58% at 2 years, approaching the tipping point for cardiologists caring for patients with advanced heart failure. Thus, the second-generation device was approved for DT based on a survival advantage over the first and, by the transitive property, on an imputed advantage over medical therapy. The previous lackluster referral for DT is no longer being blamed on the cardiology community, but instead is now retrospectively attributed to the limitations of the pulsatile devices available. Limitations of current second-generation devices may likewise come into sharper focus as we look back from the next successful innovation, perhaps the third-generation centrifugal pumps now in expanding clinical trials.

INTERMACS Registers the Acceleration of LVAD Therapy

After the milestone of the first device approval for DT, the National Heart, Lung, and Blood Institute, Food and Drug Administration, and Center for Medicare and Medicaid Services recognized the need for cartography that crossed over individual device boundaries. Interagency Registry of Mechanically Assisted Circulatory Support (INTERMACS) was formed to track and codify patient selection, outcomes, and adverse events for all patients receiving the approved implantable devices, regardless of intended duration. This registry, which has just entered patient 3400, was serendipitously positioned to capture the transition from pulsatile to continuous-flow devices and the accompanying advance in survival. Data currently available with approved devices now indicates almost 80% actuarial survival at 1 year in candidates who have not yet received transplants, although most have already undergone transplantation before the end of that year. Both the disparity between sexes and the adverse impact of age appears diminished with the nonpulsatile flow devices. Freedom from infection has improved, but the neurological events continue to occur at a rate of \( \approx 1 \) per 10 patient-years. The improvement in outcomes has both caused and reflected a shift away from the most critically ill patients since the advent of the continuous-flow devices. Because all patients currently receiving mechanical circulatory support devices are considered to have class IV symptoms, the evolution of selection has been more precisely tracked by INTERMACS profiles (Figure 1). The proportion of sickest LVAD recipients, profile 1, has declined from 46% to 21%, a trend paralleled by better renal function and nutritional status in LVAD recipients in the past year.

The use of implantable devices for DT has increased 10-fold since the approval of the continuous-flow device in January 2010 for DT (Figure 2). There has been speculation that the recent increase in DT might reflect merely a shift of patients previously named as “bridge to candidacy,” which allowed the use of the continuous-flow device when limited to potential transplant candidates. However, no decline has been registered in the bridge-to-candidacy population. Thus, there is now, for the first time, a meaningful population of patients receiving lifetime support with the continuous-flow device.

Lifetime support is the direction in which utilization of mechanical circulatory support is advancing. However, we have only just reached this milestone of acceleration, beyond which we are now traveling over unsteady ground. The current device for DT was approved based on 68% survival at 1 year and 58% survival at 2 years. Better 1- and 2-year outcomes than this have not yet been seen outside the privileged pretransplant setting, within which patients have fewer comorbidities and retain the option for transplant “rescue.” Exuberant dissemination of this technology for lifetime support could propel us backward, reminiscent of the slide down to 25% 1-year survival for cardiac transplantation in the United States after the initial success at a few expert centers. We feel that the current utilization of LVADs for DT should not accelerate further at this time, lest it move beyond the basis of evidence and the established framework of centers experienced in selection and management of patients receiving LVAD.

Who Else Should Get an LVAD for DT?

If we were to accept the argument that LVADs are still underutilized despite the recent surge in implant rate, then who are the patients who should be receiving an LVAD but currently are not? The transplant population is epidemiologically trivial, as originally emphasized by Dr Eric Rose. There are estimates between 25 000 and 250 000 of other patients who could benefit from LVAD, but we truly do not know the prevalence of heart failure with low ejection fraction in patients whose outcomes with LVAD would not be compromised by frailty, noncardiac comorbidities, right ventricular
inappropriate treatment, and limited psychosocial support. The decision-making strategy requires determination of differential risk with and without LVAD, eligibility and likely waiting times for transplantation, and patient preferences regarding lifestyle, risk, and survival. Possible routes to increased utilization could aim to pick up patients who are more sick or patients who are less sick, patients who are older, patients waiting for transplantation, and patients who could be redirected away from transplantation. Which of these directions is supported by current data?

**Levels of Illness**

**Sicker Patients?**

Among patients considered to have end-stage heart failure, the INTERMACS profiles define clinically important differences in severity of disease. There is no shortage of sick patients who have received LVADs. Nearly 70% of all registered LVADs have been implanted in patients with critical cardiogenic shock (profile 1) or progressive end-organ dysfunction despite inotropic support (profile 2). However, these worse INTERMACS patient profiles have been consistently associated with higher perioperative mortality after LVAD. In fact, over the past 2 years the field has moved away from implanting primary LVADs in patients with profile 1, the crash and burn cardiogenic shock profile, because of poor outcomes. We anticipate that most profile 1 patients will be receiving one of an array of temporary support strategies, with only a subset moving on to a durable LVAD. This would not present a good avenue down which to increase utilization of LVADs.

Profiles 2 and 3 include patients who are on intravenous inotropic infusions. A small number of similar patients formed...
the basis of the destination trials.\textsuperscript{1,4} These patients are squarely within Food and Drug Administration-approved indications for mechanical circulatory support and represent 55% of primary LVADs being implanted.\textsuperscript{10} Current use of LVAD here is already widespread and appropriate, in response to education about considering mechanical circulatory support whenever continuous inotropic infusions are contemplated.

Less Sick Patients Covered by Current Indications

If not in a sicker population, then perhaps more LVADs could be used in less sick patients than currently indicated? Patients with resting symptoms on oral therapy at home (profile 4) are already included within current reimbursed indications for LVAD (Table). Many patients who are housebound by symptoms with minimal activity (profile 5) would also be included within current reimbursed indications, if limitation is confirmed by low peak oxygen consumption (VO\textsubscript{2}). (It is noteworthy that these indications for permanent therapy actually outreached the basis of evidence at the time of approval for both the pulsatile device and the continuous-flow device, because there were too few patients not on intravenous inotropic therapy to assess the validity of the peak VO\textsubscript{2} criterion.) Until this year, fewer than 15% of patients receiving primary LVADs without biventricular support have been stable on oral therapy without intravenous inotropic support.\textsuperscript{10} The low implant rates in ambulatory heart failure (profiles 4 and 5) may have represented reluctance not only from physicians, but also from patients, who themselves did not often express willingness to consider a pulsatile LVAD while still ambulatory and walking more than 1 block and with an anticipated survival of more than 1 year.\textsuperscript{12} These preferences may soon shift with better information from the continuous-flow experience, in which 60% of 101 patients reported a moderate or greater level of function at 2 years, with average quality-of-life scores at least as good if not better than those reported after cardiac resynchronization therapy for much less sick heart failure.\textsuperscript{13} Using the class IV definition of symptoms at rest or with minimal exertion, this group already within current indications seems the most reasonable one to consider, depending on transplant eligibility, and we would join those who advocate systematic evaluation of this population for LVAD candidacy. However, we do not know the size of this group who are sick enough from their heart disease, but not too sick from residual comorbidities to live better and longer with LVADs. We will understand the size of this population better from studies such as the Medical Arm of Mechanically Assisted Circulatory Support (MEDAMACS) initiative, a parallel registry to INTERMACS of medically managed patients with advanced heart failure, for which pilot data collection is already underway.

Even Less Sick Patients—New York Heart Association (NYHA) Class III?

The walking wounded (profile 6) are comfortable at rest and during activities of daily living but nonetheless have limitation of desired activity, which varies between individuals. The role for LVAD in profile 6 and beyond is uncertain. Since REMATCH, there has been no randomized comparison of survival and functional status with LVAD against contemporary medical therapy. At the same time that LVAD technology has become streamlined and accessible, outcomes with ambulatory heart failure have improved with more targeted use of medical therapies, resynchronization therapy, and heart failure management.

When outcomes of a procedure originally tested in the sickest of the sick improve to an acceptable level, the procedure is then considered for less sick patients, who tend to have even better outcomes with the procedure, but for whom the outcome without the procedure is also better. This is the curve of downshifting risks, described initially for cardiac transplantation (Figure 3).\textsuperscript{14,15} Recent analysis of cardiac transplantation outcomes confirms that the net margin of benefit at 2 years has narrowed further, although the absolute long-term survival after transplantation has gradually improved.\textsuperscript{16}

Current trial data would not justify implantation of LVADs into patients with class III symptoms. Multiple trials of medical therapies and resynchronization pacing have shown survival rates of 70% to 80% at 2 years.\textsuperscript{17–20} The published survival with destination device therapy of 68% at 1 year and
bolic equivalents of task.13 The estimated equivalence of 4 metabolic equivalents of task is a peak VO2 of 14 mL/H12135

destination therapy; apy; star, Heartmate II destination therapy; device complications. comorbidities and the option of transplant “rescue” from populations represent a group privileged in terms of limited IV symptoms.13,21 When patients describe their own exercise class II symptoms, although some will still have class III to 360 meters, with which many patients are likely to have only walk distance from an average of 204 meters to an average of flow device has been credited with increasing the 6-minute indications for LVAD than survival alone. The continuous-benefits, if sufficiently great, could provide more compelling 1-year survival inferior to the survival expected with medical therapy for (1) the original REMATCH trial demonstrating benefit of pulsatile XVE device over medical therapy, with slightly greater benefit in patients dependent on intravenous inotropic therapy at baseline, (2) the destination device trial demonstrating benefit of the continuous-flow Heartmate II device over the same XVE device,4 and (3) recent trials of medical therapy in class III heart failure, with composite 1- and 2-year survival exceeding that currently demonstrated for destination devices.17–20 ○, class III medical therapy; star, Heartmate II destination therapy; ○, Heartmate XVE destination therapy; ●, REMATCH trial medical therapy arm. Dep indicates dependent; DT, destination therapy; HM2, Heartmate II; Ino, intravenous inotrope; Med Rx, medical therapy.

58% at 2 years for continuous-flow devices is currently inferior to the survival expected with medical therapy for class III heart failure (Figure 4). As discussed above, the 1-year survival >70% now reported for bridge to transplant populations represent a group privileged in terms of limited comorbidities and the option of transplant “rescue” from device complications.

For patients not facing imminent death, the functional benefits, if sufficiently great, could provide more compelling indications for LVAD than survival alone. The continuous-flow device has been credited with increasing the 6-minute walk distance from an average of 204 meters to an average of 360 meters, with which many patients are likely to have only class II symptoms, although some will still have class III to IV symptoms.13,21 When patients describe their own exercise ability after 2 years with continuous-flow LVADs, ≈70% describe activity levels corresponding to 2 to 4 metabolic equivalents of task.13 The estimated equivalence of 4 metabolic equivalents of task is a peak VO2 of 14 mL · kg−1 · min−1, generally considered consistent with class III symp-

toms. Although this represents a large increase compared with the bedridden or housebound patient, it may not always represent a substantial functional improvement for the patients stable with class III symptoms, for whom similarity has also been shown between cardiac transplantation and medical therapy.22 In addition, the net functional benefit of mechanical circulatory support must also be adjusted in some way for the risk of one serious stroke for every 10 patient-years.

As part of the ongoing INTERMACS effort, a parallel registry of medically managed ambulatory patients with advanced NYHA IIIIB and IV heart failure is being formed with particular focus on profiles 4 to 6 to help refine patient selection in the crucial range of ambulatory heart failure where expanded VAD utilization is anticipated. This real-world data to define the less sick patients who may benefit will complement the results of the planned REVIVE-IT study, the Randomized Evaluation of VAD InterVEntion before Inotropic Therapy.23 Until these data are available, LVAD use in the walking wounded patients may remain low, but not underutilized.

Figure 4. Survival with medical therapy and destination LVAD in clinical trials. Outcomes are aligned from (1) the original REMATCH trial demonstrating benefit of pulsatile XVE device over medical therapy, with slightly greater benefit in patients dependent on intravenous inotropic therapy at baseline, (2) the destination device trial demonstrating benefit of the continuous-flow Heartmate II device over the same XVE device, and (3) recent trials of medical therapy in class III heart failure, with composite 1- and 2-year survival exceeding that currently demonstrated for destination devices. ○, class III medical therapy; star, Heartmate II destination therapy; ○, Heartmate XVE destination therapy; ●, REMATCH trial medical therapy arm. Dep indicates dependent; DT, destination therapy; HM2, Heartmate II; Ino, intravenous inotrope; Med Rx, medical therapy.

More LVADs in Elderly Patients?
Age was the most common indication cited for transplant ineligibility in both the REMATCH and the Heartmate II DT trials, but these were still relatively young patients (mean age, 66 and 62 years, respectively).1,4 The average age of adult LVAD recipients for all indications in the United States is 51 years.10 The adverse impact of patient age is seen on both transplant and LVAD outcomes. In the overall INTERMACS cohort, the increase in age from 60 to 70 years conferred more than a doubling of early mortality risk (hazard ratio 2.42, P<0.0001), with some risk persisting late (hazard ratio 1.55, P=0.0005) after LVAD.10 Older age was the only identifiable risk factor for early mortality (2.76, P=0.03) among a smaller group of DT patients.10 The 2-fold mortality risk for patients >65 compared with 30 to 65 years remains detectable with the continuous-flow device outcomes, but the absolute difference in mortality is only half as large, because of the global improvement in survival with continuous-flow support, regardless of age.24

The average age of patients hospitalized with low ejection fraction heart failure in both the United States and Canada is ≈75 years. Nearly 75% of patients with heart failure are >65 years of age.25 There is still little information about how many older patients might do well with LVADs. Comorbidities are common in these older heart failure patients and include diabetes mellitus (36%), chronic obstructive pulmonary disease (24%), chronic kidney disease (23%), cerebrovascular disease (11%), cancer (9%), and dementia (6%).26 Because these factors could compromise perioperative and long-term outcome, the population of older heart failure patients in the community appropriate for LVAD therapy may not be large. Even in patients without major comorbidity, the interaction of age and preoperative disease severity
suggests that LVAD implantation in older patients is a procedure best performed selectively and electively.27,28

Patients Eligible for Heart Transplant

Listed Status I—Indication for LVAD

Implantable devices have totally revised the landscape of the waiting list for cardiac transplantation. Through the 1980s, the waiting list trembled under the shadows of sudden death or hemodynamic decompensation before transplantation.14 Then, implantable pacemaker/defibrillators lifted the risk of unexpected sudden death in otherwise stable patients. Subsequently, the clinical maturation of mechanical circulatory support offered rescue from spiraling shock. Elective use of mechanical support has cleared much of the burden of chronic congestion, allowing patients to enter transplantation in a state of good nutrition, renal and hepatic function, and physical strength. Since 1999, >one third of all listed adult heart transplant candidates and 75% of those initially listed as status I have been supported with an LVAD.29 Early consideration for LVAD may be indicated for the other status I patients who now wait with indwelling pulmonary catheters and inotropic infusions. Although status I was conceived to be for patients unlikely to survive for 7 days, the average wait for status I patients in some regions has paradoxically increased to beyond 6 months, during which they face line sepsis, venous thrombosis, pulmonary emboli, and decubiti, in addition to exhaustion of family support resources while in the hospital. When RV function is adequate, status I patients could probably be served best by increased use of LVADs to allow them to return home. Thus, the status I transplant candidate population represents a small but highly visible niche in which LVADs may indeed be currently underutilized. However, addressing this group would not substantially increase the number of LVAD implants; there are only 2200 transplants annually in the United States and many status I patients without LVADs may deteriorate to receive them urgently anyway.

Status II Candidates for Transplantation

The role for LVAD in patients listed in status II for heart transplant is more opaque. With limited donor organ availability and longer waiting times, only 14% of all patients receiving transplants in 2009 received transplants as status II.29 Status II survival without transplant, although biased by censoring for LVAD or urgent transplant, has been surprisingly good, with 81% 1-year survival and 74% 2-year survival 2000 to 2005.16 Improved outcomes may reflect both better medical therapies and earlier listing when status II time was worth accumulating, but have occurred despite increasing age at listing and a greater burden of comorbidities.16 Although these survival rates are similar to the current best LVAD outcomes, LVAD might substantially improve functional capacity and quality of life compared with the waiting list.

Early referral for device therapy may also be reasonable in those patients listed for transplant anticipated to have a long wait, such as those with blood type O, large body size, or high sensitization with anti-HLA antibodies. For all of these current or potential candidates, quality of life may well be enhanced by moving out from the shadow of the waiting list, with its oppressive restrictions on life, and by accepting LVAD as primary therapy. Speculating about the near future, it may be that transplantation will be best reserved for those candidates who have dominant RV dysfunction or other structural obstacles to left heart support. In the distant future where most eligible patients are living good lives on mechanical support, prolonged cardiac preservation might even allow hearts to be allocated on the basis of HLA matching.

The Role for LVADs in Marginal Transplant Candidates

Reference to the original cardiac transplantation selection criteria reveals that the majority of patients currently listed now for transplantation have conditions once considered as contraindications. Inexplicably, we continue to allow progressive widening along the Möbius strip of the waiting list even as it elongates. Although most obvious for age, this is true also for renal dysfunction, hepatic dysfunction, pulmonary disease, diabetic complications, and psychosocial limitations. One proposal has been the use of an alternate waiting list strategy to maximize donor utilization. In comparison, survival with pulsatile LVAD was similar to survival for extended donor criteria transplant recipients at 1 year despite greater preoperative instability in the LVAD group.30 LVADs have been proposed as a bridge to candidacy for some marginal recipients with potentially reversible contraindications.31 Current evidence suggests that reversibility of contraindications after LVAD may be relatively low except in the acutely decompensated patient. Although encouraging data exist for the reversal of secondary pulmonary hypertension in select patients,32–34 mechanical support does not appear adequate to reverse RV dysfunction in most VAD recipients.35 Many marginal transplant candidates who receive LVAD as bridge to a decision about transplant candidacy will be shifted to lifetime support with an LVAD, but this requires a firm recalibration of expectations. Just as for the transplant candidates discussed above, implantation of an LVAD as primary therapy rather than a bridge to something else may be the more realistic and rewarding context. In addition, allocation of scarce donor hearts has always presented serious challenges to our concepts of distributive justice. A truly equal-access mechanical alternative can lift us above these dilemmas to focus on selecting the best therapy for the patient, rather than selecting the best patient for the therapy, within a broader framework of overall healthcare budget restraint. Thus, we propose that the offer of primary LVAD therapy to marginal candidates for transplantation does present an avenue for increased LVAD utilization, even though it is not likely to increase dramatically the number of recipients.
**Selecting Patients for Lifetime Therapy**

With the considerations above, it is challenging to locate the intersection of patients who face high mortality without LVAD and yet can look forward to good outcomes with LVAD.31 This is even more challenging as long as the search is directed toward patients who have absolute contraindications to transplantation. The excellent outcomes with devices have been achieved in highly selected patients. The 58% 2-year survival with the continuous-flow device was in patients carefully selected for a low-to-medium DT risk score (mean, 10).4,5,36

Accurate assessment of RV function is crucial to utilization of LVADs in patients for whom transplant is not an option, because mechanical biventricular support is not yet feasible for long-term support. Multiple RV failure clinical risk scores have been developed, although none were derived in a DT cohort or with the newer nonpulsatile LVADs, which may be even more sensitive to RV failure.37,38 RV failure results in up to a 6-fold increase in death with LVAD.37 With current protocols, RV dysfunction seen on inotropic support before LVAD appears to persist after LVAD, with unknown long-term consequences.35 The number of patients in whom RV dysfunction should preclude isolated left ventricular support is not known.

**LVAD Complications—Expecting the Unexpected**

Lessons from black swan events teach us that we place too much trust in our ability to predict the future from the past; we forget our former failures to predict the recent past from the earlier past.39 Animal models did not teach us enough about how to predict device thrombogenicity, and the human bridge trials did not teach us about the pulsatile device failures that were then seen in the destination trial. Relying more firmly on clinical experience rather than extrapolation, we need to ensure that we can collect and process information in real time as we move forward. Danger exists of doing harm if LVAD use accelerates beyond our current knowledge of how to deploy this technology effectively.

The approved pulsatile device for DT did not require the routine anticoagulation now needed for nonpulsatile flow. However, the risk and type of bleeding with nonpulsatile flow was not anticipated.40 Gastrointestinal bleeding has been frequent, and may be related to de novo arteriovenous malformations or an acquired von Willebrand’s deficiency.41,42 Another unexpected challenge with continuous flow has been the chronic development of aortic valvular insufficiency.43 Some surgeons now consider suturing of the aortic valve at the time of LVAD implant.44 With a permanently closed aortic valve, the native ventricle no longer offers the reassurance of a back-up pump, and the LVAD is truly replacing rather than assisting the ventricle. More routine aspects of managing nonpulsatile flow have proven unexpectedly complicated.45 Maintaining adequate pump speed, circulating volume, and antihypertensive therapy has been challenging as we learn to interpret vital signs in the absence of a pulse.46

We continue to face the inherent risks of infection and stroke. Late driveline infection has been described as the Achilles heel of prolonged LVAD support.47 The most dreaded complication of mechanical circulation is debilitating strokes, which remain as common with continuous as with pulsatile devices.4 The overall stroke rate most recently published is 0.13 events per patient-year.3 The optimum duration and intensity of anticoagulation and antiplatelet therapy during LVAD support has yet to be defined. As we move forward to offer these devices to patients with an anticipated 70% 1-year survival without VAD, a 1 in 10 incidence of major stroke is a formidable risk.

**More LVADs Where?**

Just as cardiac transplantation provided the infrastructure for LVAD development, utilization of LVAD therapy is only feasible within an integrated program of care offering all options, including optimization of medical and pacing therapies, evaluation for transplantation, and, when appropriate, a focus on patient preferences for end-of-life care. Competing demands for constrained hospital resources may limit the training and retention of the trained personnel required for successful outcomes and for accreditation. In addition to cardiac surgery and cardiology, certification for an LVAD program requires committed staff in infectious diseases, psychiatry, palliative care, social work, nutrition, financial counseling, and a dedicated inpatient and outpatient nursing team; all are mandatory. For example, a ratio of one dedicated VAD coordinator (for which a trained circulatory equipment technician may substitute as one coordinator in a large program) to ≈15 LVAD patients has been proposed as an informal benchmark. Rapid growth in LVAD use coupled with improving outcomes has already led to large outpatient LVAD clinics. The space requirements alone for the staff and equipment are daunting, requiring sustained programmatic commitment from the hospital administration. If the number of implants were to accelerate further, where would they go? There are currently 81 programs approved to provide LVADs for DT. While welcoming the progress, many of these centers are not yet adequately staffed for the acceleration already underway.

Rapid dissemination of this complex therapy into less experienced centers could undermine the projected good outcomes and defer ascent along the steep learning curves. Center experience and procedural volume has been shown to be of critical importance given the complexity of patient care with LVADs.48 As we learned with transplantation, the majority of patients referred can enjoy prolonged good quality of life with expert redesign of their medical regimen; such patients should not undergo the risk of LVADs to support an institutional volume metric. It is highly likely that some ideal LVAD candidates are being overlooked because of geographically limited access to health care. However, in
settings with such limited resources, the first investment should be into heart failure management to provide recommended therapies for earlier stages of heart failure, which will always affect more people than will be eligible for replacement therapies.

Conclusion
Improvements in survival and quality of life after LVAD have moved us into a new era of mechanical circulatory support for advanced heart failure. All of our efforts will be needed to maximize outcomes and learn from the experiences offered in the current acceleration wave of increased utilization. In this era, increase in LVAD implantation may be most appropriate as an alternative to transplantation in patients for whom candidacy is uncertain or marginal, or for whom function and quality of life could be better served by circulatory support as primary therapy rather than by a long waiting list. We would also support ongoing initiatives to better define the size of the ambulatory patients with resting symptoms for whom right ventricular dysfunction and comorbidities do not preclude good quality survival with LVADs. However, there is not sufficient evidence at this time to increase LVAD utilization in more sick patients, less sick patients, or much older patients. Further acceleration could jeopardize the progress already made and derailed the projected future. In an era where resource utilization is under stern scrutiny, we must drive beyond efficacy alone. Cost-effectiveness will require timely implants in carefully selected patients at the centers most experienced at delivering this complex therapy within the framework of overall heart failure management.

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Response to Stewart and Stevenson

Leslie W. Miller, MD

The article by Stewart and Stevenson seeks to rationalize a limited increase in the use of ventricular assist devices (VADs) by analyzing selective cohorts of patients. However, the focus of the debate should be on the estimated 100 to 300,000 deaths per year due to heart failure (HF), which includes a 33% mortality rate after a single HF hospitalization and increases with each subsequent admission. Even the most conservative estimates suggest that there are >100,000 patients with advanced or end-stage HF, and only 3000 VADs are implanted each year. Increased utilization of VADs should not be focused as much on expansion from current indications into patients with less severe HF, but on the large number of patients that meet current guidelines who are not being referred for evaluation for advanced therapies such as VADs.

The primary end point of clinical trials with VADs to date has been survival, rather than the more appropriate combined end point of objectively measured improvement in functional capacity and quality of life, the two major concerns of patients with advanced heart failure, both of which were significantly increased in recent trials in both bridge to transplant and destination therapy patients.

The new generation of continuous-flow left ventricular assist devices has brought an entirely new level of durability and patient comfort, as well as a reduction in adverse events, which together have resulted in very significant improvement in survival over the first generation of devices. Clinicians adopt a new technology when there is a body of evidence to demonstrate superiority over previous strategies. The recent trial data provide the basis for a significant increase in the utilization of VADs in selected patients with advanced HF.
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