A Bridge Far Enough?

Lynne Warner Stevenson, MD; Sharon A. Hunt, MD

The publication in this issue of Circulation of the Evaluation of the HeartWare Left Ventricular Assist Device for the Treatment of Advanced Heart Failure (ADVANCE) trial by Aaronson, Slaughter, and colleagues tracks continuing advance in the rapidly expanding field of mechanical circulatory support. As implantable device technology and the clinical learning curve have supported better outcomes over time, the journey is leaving the critically ill patients behind and moving into populations with less imminent risk of death, and will soon include more ambulatory patients for whom pivotal outcomes extend beyond stroke-free survival.

The success of this trial stimulates questions about routes to new device approval, the length of our bridges, and the directions for travel beyond a bridge.

About Circulation

Editorial

Control Populations for Bridging

The ADVANCE trial demonstrated that the new continuous flow centrifugal device serves as an effective bridge for patients awaiting a donor heart for transplantation. Previous devices approved for this indication include several configurations of pulsatile pumps and most recently a continuous flow axial pump. Approval for the bridging indication has required progressively more rigorous data but has never been supported by a randomized trial, because randomization to death or to device support is not reasonable in the face of progressive organ compromise and anticipated death from native heart collapse. Of the first 3 devices approved for the bridging indication, 2 offered no control population and 1 included a small historical control of patients in the same institutions who, for various reasons, did not receive a device.

The present report raises the standard for bridging device approval, offering the first prospective comparison of outcomes with the new device with outcomes without it during the same time period, in this case with other devices currently available for left ventricular support.

The control data population was drawn from the Intergroup Registry for Mechanically Assisted Circulatory Support (INTERMACS) Registry, which chronicles the progress of durable mechanical circulatory support throughout the United States, growing from ≈1000 patients in 60 sites at the initiation of the ADVANCE trial in 2008 to 3500 patients at the conclusion of this trial and 5500 in 150 sites at the time of this publication. The original registry design included detailed characterization of measured baseline characteristics and the INTERMACS profiles, which are descriptors of clinical disease severity that include the time dimension of increasing acuity (Figure). These require experienced clinical assessment and are quantitatively less rigorous than laboratory values. They have, however, served to classify subpopulations previously described broadly as New York Health Association Class IV into smaller groups with distinct outcomes. Because of their high early mortality after implantation of durable devices, patients with the greatest acuity of illness, the crash and burn Profile I, now usually receive short-term temporary support devices until stabilized for implantation of the durable devices intended for discharge and long-term use.

The criteria for selection of patients in the investigational device trial were the same as criteria for selection of the control patients from the INTERMACS registry. The end points of death and transplantation in this control group were provided from the INTERMACS registry. Specific adverse events, independent from impact on the trial end points, were determined for the investigational device with common event definitions. However, the comparison with contemporary national data was not designed to align specific adverse events from the investigational device with INTERMACS adverse event reports. These differ in both nature and frequency between devices and can be specified for general type but not brand of device.

Although characteristics for secondary organ function were carefully specified, the baseline characteristics for inclusion did not align the proportion of INTERMACS profiles. Patients for an investigational trial can be more carefully selected to avoid those perceived at higher general risk of postoperative complications. Profile I patients accounted for <10% in both the control and investigational arm, whereas Profile 2 patients (“Sliding on inotropes”) accounted for 52% of the control arm but only 24% of the investigational arm, in whom, conversely, there was a higher proportion of the more stable Profile 3 patients, 52% versus only 21% in the control arm. Thus, the population in the trial arm represented an unintended bias toward less acuity of disease. Although this has been of some concern, the post hoc comparison divided into INTERMACS profiles indicated equivalent outcomes between the 2 arms for each profile.

A New Benchmark for Approval?

The data presented in this study are convincing for noninferiority of the new device for this indication. Potential advantages of the newer device include its smaller size and more durable design, but there is no evidence provided here that
would indicate superiority compared with current axial flow technology. With a feasible device trial size, it would in fact be difficult to demonstrate superiority over a 90% success rate for transplantation or survival at 6 months with the original device.

The current trial establishes a 90% benchmark for success with current and new technology. This benchmark represents a formidable target for approval of other devices. The presumed indications for support by virtue of disease severity are underwritten by the requirement for patients to be eligible and waiting for transplantation. For this specific population, it may be feasible to simplify the initial approval for future devices by specifying this benchmark, without requiring direct comparison with control groups on other devices or on medical therapy. Continued tracking of the INTERMACS outcomes could perhaps serve as contemporary surveillance to determine when the benchmark of success for the bridging indication should be raised.

**A Short Bridge**

The journey with this device was for most patients a short one. The outcome of ongoing device support for 6 months is known for only 88 of the 140 patients receiving the device, because many underwent heart transplantation before that time. It is difficult to estimate the adverse event rates that would be seen with longer support. There were 6 pump exchanges in <180 days. If the ischemic and hemorrhagic strokes documented are in unique patients, the rate of stroke was 10% at 30 days, and gastrointestinal bleeds, seen with increasing frequency now with all continuous flow devices, occurred in 11% of patients during the trial period.

Differences between the trial experience and the actual clinical use with this device for the bridging indication will arise from the long tail of transplant waiting times in some United Network for Organ Sharing regions, often longer than 1 year and sometimes longer than 2 years, unless device complications warrant an escalation of priority status for transplant. Prolonged duration of support on a bridging device will result also from the ambiguity of transplant candidacy. Although device approval and indications have been artificially dichotomized into bridge to transplant and “destination” or lifetime support, 40% of patients receiving implanted devices have been categorized as neither listed for transplant nor planned for destination therapy, but instead as bridge to candidacy. In 2011, for the first time, the number of patients described as bridge to candidacy exceeded those listed for transplant at the time of device implantation. Teuteberg and Stewart have shown that the rate of transplantation by 12 months is 40% for patients with initial intent of bridge to candidacy, and 20% for those with stated intent of bridge to candidacy who were nonetheless initially deemed unlikely to become eligible for transplantation. It is anticipated then that a substantial propor-

![Clinical Decisions For Support](image-url)
tion of patients receiving devices approved for the bridge indication will transition to lifetime support, for which the outcomes with this device are not known.

The Life-Time Journey
The initial conception of mechanical circulatory support was that it would provide prolonged support, variously described as permanent, life-time, or destination therapy. As the inherent limits of the supply of donor hearts were becoming evident, the goal was to provide a nonbiological alternative to replacement of the failing heart. The strategy of bridging transplant candidates to donor availability was not part of this original construct but rapidly became the laboratory or clinical proving ground for device development and initial approval. Experience has shown that the data provided in this bridging laboratory do not necessarily predict the outcomes or adverse events with the same devices used over a longer duration. To date, the trials supporting approval of devices for lifetime therapy have all included randomized comparator groups, unlike the bridging indication. The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial of the bridging pulsatile device used for destination therapy demonstrated a 2-year survival of only 23%. Although significantly better than the 8% survival on medical therapy, this fell short of expected device durability, in part because of the unanticipated high failure rate of the inflow valve during prolonged use. Extrapolation of other adverse events from short duration support to longer support may also be misleading, as the risks are not necessarily constant over time from implantation. From the current trial, the rate of stroke (embolic or hemorrhagic) per person-year may be as high as 16% and the rate of gastrointestinal bleeding as high as 23%, but true rates observed in longer follow-up will be crucial to determine.

Lifetime support is the ultimate value added by mechanical circulatory support technology. Although there is clear benefit for individuals from a bridging device that supports survival with better organ function and nutrition until transplantation, the benefit to the overall heart failure population is less clear as transplant waiting times continue to lengthen. The shuffling of hearts among transplant candidates according to ability or complications on the device does not ameliorate the donor shortage. For some patients, travel to a region with shorter waiting times may present less risk than an additional sternotomy and cardiopulmonary bypass to receive a bridging device.

For patients receiving devices, focus toward the future exchange of the device for a heart transplant may diminish the realization of improved function and quality of life offered in the present by mechanical circulatory support. Patients and families continue to calibrate their expectations to the normalcy expected from transplantation. Life lived until is often not lived to its fullest.

Information Needed for Shared Decision-Making
Now that early to intermediate survival is expected with mechanical circulatory support, the eligible populations have expanded beyond those at imminent risk of death. As we move into the less sick populations of INTERMACS profiles 4 and 5 of ambulatory heart failure (Figure), there is increasing scope for individual patient preferences to influence decisions about mechanical circulatory support devices. A majority of ambulatory patients with heart failure report that expected quality of life and functional capacity would be equal in importance to expected survival with implanted devices when making such a decision.

The functional capacity and quality of life reported in this trial are encouraging, as has been reported also for the continuous axial flow devices. The 6-minute walk distance in this trial improved markedly from a baseline at which >half of patients had an imputed value of 0 as unable to walk. The quality of life achieved was comparable with that achieved after cardiac resynchronization therapy in a healthier population at baseline. However, ~10% of patients in the current study did not have baseline quality of life data, and almost half did not have follow-up assessments. The rigor of functional data collection has continued to lag beyond the assessment of mortality end points but will intensify now that the survival benchmark is high. Additional information needed for informed decision-making will include the nature and magnitude of caregiver burden, particularly for the older population.

The success of this initial experience with the centrifugal pump has stimulated excitement about the longer-term outcomes with this device in this population. After approval of this new device, these data will accumulate rapidly from all implanting centers around the country, as happened after approval of the continuous rotary flow device. Current approved indications for reimbursement have included patients at home on oral medications with heart failure symptoms at rest or minimal exertion, as supported by measurement of peak oxygen consumption <12 to 14 mL/kg/min. However, the excellent results from this trial encourage optimism that benefit could also be realized with this continuous centrifugal flow device implanted in patients with less limitation of function and survival earlier in the course of heart failure progression (Figure 1). There are plans to test this hypothesis in the National Heart, Lung, and Blood Institute-sponsored Randomized Evaluation of VAD Intervention Before Inotropic Therapy (REVIVE-IT) trial.

The complexity and breadth of new technology impose major responsibilities on those in a position to deploy it. Mechanical circulatory support can only be offered in the context of integrated care for heart failure that includes experienced medical and rhythm device therapy and the spectrum of palliative care options. A recent report has illuminated the challenges around how to quantitate and communicate information about a ventriculally assist device for life-time therapy, while eliciting and listening to patient values, goals, and preferences. This must be done recognizing and validating that saying “No” to the dramatic intervention is sometimes the right decision for a patient to make, while endorsing saying “Yes” for maintenance of the ongoing physician-patient relationship and supportive care options. As resources are increasingly constrained, decisions will have to be made also about the optimal allocation of human and...
hospital resources to manage mechanical circulatory support and to support the many heart failure patients who will be managed without devices during their journey.

Disclosures
Dr Stevenson is a co-principal investigator for the National Heart, Lung, and Blood Institute–sponsored INTERMACS Registry, HHSN268201100025C.

References

KEY WORDS: Editorials □ heart failure □ heart transplantation
A Bridge Far Enough?
Lynne Warner Stevenson and Sharon A. Hunt

Circulation. 2012;125:3069-3072; originally published online May 22, 2012; doi: 10.1161/CIRCULATIONAHA.112.111948

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/125/25/3069