After nearly 50 years of clinical development, durable mechanical circulatory support (MCS) devices are widely available for patients with advanced heart failure. The field of circulatory support has matured dramatically in recent years, thanks to the advent of smaller, rotary pumps. The resulting transition away from older pulsatile devices has been swift. Accelerated use of continuous-flow left ventricular assist devices (LVADs) for long-term support has changed the face of advanced heart failure care. MCS candidate selection, risk stratification, and management strategies are evolving in tandem with new pump technology, producing a shift in the profiles of patients being considered for MCS. Timely referral for MCS evaluation and appropriate implantation now depends on familiarity with recent advances in pump design and clinical outcomes. This review, the first in a series on Advances in Mechanical Circulatory Support, will focus on durable intracorporeal LVADs used in adults with advanced heart failure, and highlight the evolution in both patients and technology.

History of Mechanical Circulation
The modern era of cardiac surgery began in 1953 with the first clinical use of cardiopulmonary bypass, allowing increasingly complex operations and laying the foundation for circulatory assist devices. Shortly after its invention, the heart-lung machine began to be used to support patients with postcardiotomy cardiogenic shock to facilitate recovery after failed operations. By the 1960s, simple cardiac assist devices began to replace cardiopulmonary bypass for the treatment of postcardiotomy shock (Figure 1). The first clinical use of an implantable artificial ventricle was reported by Liotta et al2 in 1963. This primitive ventricular assist device (VAD) consisted of a pneumatically driven, tubular displacement pump with a valved conduit connecting the left atrium to the descending thoracic aorta. The pump provided partial left ventricular bypass for 4 days after postoperative cardiac arrest before the patient died of multiorgan failure. Inspired by this pioneering work in cardiac surgery and encouraged by results from large animal experiments, the National Institutes of Health (NIH) established the Artificial Heart Program in 1964,3 and 6 companies were contracted to assess the engineering feasibility of such a device. By 1966, the first successful pneumatic LVAD had been used by DeBakey to support a patient for 10 days after complex cardiac surgery.4

Shortly after the first human heart transplant by Barnard in 1967, artificial ventricle technology began being used as a mechanical bridge to support patients with postcardiotomy shock until a donor organ could be identified. Cooley et al5 reported the first use of a total artificial heart as a bridge to transplant (BTT) in 1969. Ever since, the fields of mechanical circulation and cardiac transplantation have evolved in counterpoint to each other. Despite the early promise of human heart transplantation, in the 1970s, high mortality rates early posttransplant attributable to inadequate immunosuppression further spurred on the development of MCS. However, the first generation of extracorporeal pneumatic LVADs of the 1970s could only be in place for a matter of days. These pumps had a traumatic blood interface leading to hemolysis and thrombosis, as well as inadequate power supply, faulty control mechanisms, and prohibitive cost. These limitations prompted the NIH to issue another series of initiatives in the late 1970s to develop component technology for deployment in durable implantable assist devices intended for use in chronic heart failure.

The apogee of popular interest in mechanical circulatory replacement came in 1982 after Barney Clark, a Seattle dentist, received the Jarvik-7 total artificial heart (TAH). This was the first device intended for permanent circulatory support and allowed the recipient to survive 112 days before dying of sepsis.6 TAH development eventually stalled because of high rates of infection, pump thrombosis, and stroke. Meanwhile, the MCS community redoubled efforts to design simpler, single-chamber pumps that could act as assist devices in series with the native ventricle. In addition, cardiac transplantation experienced a renaissance after the US Food and Drug Administration (FDA) approved cyclosporine in 1983. Improved immunosuppression featuring a calcineurin inhibitor contributed to a sharp increase in graft survival and a rapid expansion in the number of heart transplant programs in the United States.7 Hopes for artificial circulation persisted thanks to the collaborative efforts of intrepid surgeons, innovative engineers, and courageous patients. The NIH-
sponsored programs for long-term support bore fruit in 1984
with successful deployment of the electric, pulsatile Novacor
LVAD as a BTT.8 That same year the Centers for Medicare and
Medicaid Services codified distinct strategies for me-
chanical support to guide device development and regulatory
approval (Table 1). By the mid-1990s, FDA had approved
multiple pulsatile platforms allowing patients to recover from
postcardiotomy shock or bridge to cardiac transplant.8

The expansion of durable LVAD options for patients with
advanced heart failure came just as the significant shortage of
donor hearts was becoming apparent. The advanced heart
failure epidemic in the United States has been estimated to
include 100 000 to 250 000 patients with refractory New
York Heart Association (NYHA) class IIIB or IV symptoms.9
Yet <2300 donor hearts are available and reserved for highly
selected, younger candidates with limited comorbidities.10

Figure 1. Historical perspective on mechanical circulatory support. This timeline marks the seminal events in mechanical circulatory support over the previous 5 decades, from the first reported use of an artificial ventricle in 1963 to the current generation of continuous-flow pumps. ADVANCE indicates Evaluation of the HeartWare Ventricular Assist Device for the Treatment of Advanced Heart Failure; CMS, Centers for Medicare and Medicaid Services; FDA, Food and Drug Administration; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; NHLBI, National Heart, Lung and Blood Institute; NIH, National Institutes of Health; NYHA, New York Heart Association; REVIVE-IT, Randomized Evaluation of Ventricular Assist Device Intervention before Inotrope Dependence; TAH, total artificial heart; and VAD, ventricular assist device.

Table 1. Implant Strategies and Target Populations for Mechanical Circulatory Support

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Definition</th>
<th>Target Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bridge to transplant (BTT)</td>
<td>For patients actively listed for transplant that would not survive or would develop progressive end-organ dysfunction from low cardiac output before an organ becomes available.</td>
<td>Patients with progressive end-organ dysfunction or refractory congestion, those anticipated to have a long waitlist time (eg, highly sensitized, blood group O), or who desire improved quality of life while waiting.</td>
</tr>
<tr>
<td>Bridge to candidacy (BTC)</td>
<td>For patients not currently listed for transplant, but who do not have an absolute or permanent contraindication to solid-organ transplant. This includes patients in whom potential for recovery remains unclear.</td>
<td>Patients who might be eligible for transplant after a period of circulatory support that allows for improved end-organ function, unloading (eg, pulmonary vasodilation) or nutrition, resolution of a comorbid condition (eg, cancer treatment) or institution of lifestyle changes (eg, weight loss, smoking cessation).</td>
</tr>
<tr>
<td>Destination therapy (DT)</td>
<td>For patients who need long-term support, but are not eligible for transplant because of one or more relative or absolute contraindications.</td>
<td>Older patients (eg, &gt;70 y) or those with multiple comorbidities anticipated to require only left ventricular support.</td>
</tr>
<tr>
<td>Bridge to recovery (BTR)</td>
<td>For patients who require temporary circulatory support, during which time the heart is expected to recover from an acute injury, and mechanical support is then removed without need for transplant.</td>
<td>Patients with reversible cardiac insults such as post–myocardial infarction or post–cardiotomy shock, fulminant myocarditis, or peripartum cardiomyopathy.</td>
</tr>
</tbody>
</table>
Evolving Flow Profile

For lifelong support in transplant-ineligible patients.12,13 With the continuous-flow HeartMate (HM) II for DT in 2010, there has been a 10-fold increase in approved LVADs implanted to map the evolution of durable MCS. Since the approval of the HM XVE for permanent destination therapy, there have been continuous-flow pumps implanted to study the impact of continuous-flow circulation. The ADVANCE (2010) study enrolled NYHA class IV patients ineligible for transplant and directly compared flow profiles. Superior survival was seen with the continuous-flow profile compared with the pulsatile profile (Table 2).15 The INTERMACS registry confirmed the superior survival with continuous-flow pumps at 1 year (83% versus 67%) and 2 years (75% versus 45%), with an overall P < 0.0001.13 Although continuous-flow pumps increase the probability of survival to transplant, once a patient receives a transplant, survival is similar regardless of whether a pulsatile or continuous-flow pump was used.

Pumps in Evolution

Evolving Flow Profile

In the field of assisted circulation, evolving pump design has driven clinical progress (Table 3). After the invention of a smaller high-speed, rotary impeller pump with a single moving part, continuous-flow VADs with enhanced durability and near-silent operation became available. The transition from pulsatile technology toward continuous flow has been remarkably swift. Before 2008, all VADs implanted in the United States were continuous flow.13

Although LVAD technology was pioneered in the bridge setting where transplant offered a bailout for device failure, as devices matured, development began to be targeted toward devices capable of long-term or permanent circulatory support.11

Over the past 2 decades, a series of revolutions in pump design and pivotal clinical trials have changed the face of advanced heart disease care (Table 2). The landmark FDA approval of the HM XVE for permanent destination therapy (DT) in 2003 uncoupled access to durable MCS from transplant eligibility. As VAD therapy entered the mainstream, the collaborative Interagency Registry of Mechanically Assisted Circulatory Support (INTERMACS) was established in 2006 to map the evolution of durable MCS. Since the approval of the continuous-flow HeartMate (HM) II for DT in 2010, there has been a 10-fold increase in approved LVADs implanted for lifelong support in transplant-ineligible patients.12,13 With 1-year survival now >80% with the approved continuous-flow LVAD, the promise of half a century’s work has been realized, and “the decade of the ventricular assist device”14 has arrived.

Table 2. Landmark Trials in Mechanical Circulatory Support

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Strategy</th>
<th>Device</th>
<th>Flow Profile</th>
<th>Population</th>
<th>Design (n)</th>
<th>Primary End Point(s)</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>REMATCH (2001)</td>
<td>DT</td>
<td>Thoratec HeartMate XVE</td>
<td>Pulsatile</td>
<td>NYHA class IV, LVEF ≤0.25 with VO2 ≥12 mL·kg⁻¹·min⁻¹ or inotrope dependent; ineligible for transplant</td>
<td>Randomly assigned 1:1 to HeartMate XVE (68) vs optimal medical management (61)</td>
<td>Death from any cause</td>
<td>48% reduction in death with LVAD vs medical therapy (P &lt; 0.001); overall survival at 1 year 52% with LVAD vs 25% with medical therapy (P &lt; 0.002)</td>
</tr>
<tr>
<td>Total artificial heart (2004)</td>
<td>BTT</td>
<td>SynCardia CardiWest TAH-t</td>
<td>Pulsatile</td>
<td>Transplant eligible; risk of death from biventricular failure</td>
<td>Nonrandomized TAH at 5 centers (61) vs historical controls (35)</td>
<td>Survival until transplant; overall survival</td>
<td>Survival to transplant 79% with TAH-t vs 46% controls (P &lt; 0.001); overall survival at 1 year 70% with TAH vs 31% controls (P &lt; 0.001)</td>
</tr>
<tr>
<td>HeartMate II BTT (2007)</td>
<td>BTT</td>
<td>Thoratec HeartMate II</td>
<td>Continuous (axial)</td>
<td>NYHA class IV; listed for transplant UNOS status 1A or 1B</td>
<td>Nonrandomized (133), without controls or comparison group</td>
<td>Proportion transplanted, listed or eligible to be transplanted, or recovery with explant by 180 days</td>
<td>75% met primary end point (42% transplanted, 32% alive with ongoing device support, 1% recovered)</td>
</tr>
<tr>
<td>HeartMate II DT (2009)</td>
<td>DT</td>
<td>Thoratec HeartMate II and HeartMate XVE</td>
<td>Continuous (axial) and Pulsatile</td>
<td>NYHA class III or IV; LVEF ≤0.25 with VO2 ≤ 14 mL·kg⁻¹·min⁻¹ or ≤ 50% predicted; ineligible for transplant</td>
<td>Randomized 2:1 to HeartMate II (134) vs HeartMate XVE (66)</td>
<td>Survival at 2 years free of disabling stroke or reoperation for device repair or replacement</td>
<td>Composite end point in 46% with HeartMate II vs 11% with HeartMate XVE (P &lt; 0.001); Actuarial survival at 2 years 58% vs 24%, respectively</td>
</tr>
<tr>
<td>ADVANCE (2010)</td>
<td>BTT</td>
<td>HeartWare HVAD</td>
<td>Continuous (centrifugal)</td>
<td>NYHA class IV; listed for transplant UNOS status 1A or 1B</td>
<td>Nonrandomized HVAD (137) vs contemporary LVAD registry controls (499)</td>
<td>Proportion alive or transplanted at 180 days compared with registry controls (propensity score adjusted)</td>
<td>Alive or transplanted: 92% of HVAD vs 96% of controls (P = 0.001 for noninferiority)</td>
</tr>
</tbody>
</table>

ADVANCE indicates Evaluation of the HeartWare Ventricular Assist Device for the Treatment of Advanced Heart Failure; BTT, bridge to transplant; DT, destination therapy; HVAD, HeartWare ventricular assist device; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; REMATCH, Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure; TAH-t, temporary total artificial heart; UNOS, United Network of Organ Sharing; and VO2, peak oxygen consumption.
Table 3. Implantable LVADs in Evolution

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>HeartMate XVE</th>
<th>Thoratec IVAD*</th>
<th>HeartMate II</th>
<th>HeartWare HVAD</th>
<th>Jarvik 2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow profile</td>
<td>Thoratec</td>
<td>Thoratec</td>
<td>Thoratec</td>
<td>HeartWare</td>
<td>Jarvik Heart</td>
</tr>
<tr>
<td>Implant site</td>
<td>Abdomen</td>
<td>Abdomen</td>
<td>Abdomen</td>
<td>Pericardium</td>
<td>Pericardium</td>
</tr>
<tr>
<td>Driver</td>
<td>Electric</td>
<td>Pneumatic</td>
<td>Electric</td>
<td>Electric</td>
<td>Electric</td>
</tr>
<tr>
<td>Weight</td>
<td>1150 g</td>
<td>339 g</td>
<td>290 g</td>
<td>160 g</td>
<td>90 g</td>
</tr>
<tr>
<td>Displacement</td>
<td>400 mL</td>
<td>252 mL</td>
<td>63 mL</td>
<td>50 mL</td>
<td>25 mL</td>
</tr>
<tr>
<td>FDA approval</td>
<td>BTT, DT</td>
<td>BTT</td>
<td>BTT, DT</td>
<td>IDE</td>
<td>IDE</td>
</tr>
</tbody>
</table>

BTT indicates bridge to transplant; DT, destination therapy; FDA, Food and Drug Administration; HVAD, HeartWare ventricular assist device; IDE, investigational device exemption; and IVAD, implantable ventricular assist device.

*Thoratec PVAD is the same pump placed in a paracorporeal position.

Continuous-flow LVAD is used as a bridge.16,17 Furthermore, although older data have shown impaired posttransplant survival in patients bridging with LVADs,18 a new International Society for Heart and Lung Transplantation report shows similar outcomes in comparison with patients who do not require pretransplant LVAD support.17

Interestingly, both REMATCH and the HM II DT trial showed similar 50% to 60% 1-year survival with the XVE device despite nearly a decade of intervening clinical experience, suggesting a limit to further long-term progress with approved pulsatile LVAD technology.19 In contrast, there has been a notable temporal improvement in survival to transplant with the HM II in recent years. In the extended enrollment phase of the pivotal trial, 1-year survival increased from 68% to 74% in comparison with the original cohort, then increased further to 85% in the postapproval setting.20,21 The apparent learning curve after adoption of continuous-flow technology may be attributed to improved patient selection, surgical experience, and postoperative medical care. Management suggestions have been published for in-hospital and longitudinal management of LVADs, although the brisk pace of change in the field has precluded development of consensus guidelines.22–24

Smaller rotary pumps like the HM II have some unique benefits beyond improved survival. The lower pump profile allows preperitoneal abdominal implantation in somewhat smaller patients, including women and adolescents. Before the HM II, patients with small body surface area were relegated to an extracorporeal pump as a BTT and had no approved DT option that could safely fit in their abdomen. Smaller pump profiles also have been linked to earlier postoperative recovery and enhanced comfort due to less crowding. The newer HeartWare VAD (HVAD) and Jarvik-2000, which are still under investigation, are small enough to allow intrapericardial implantation, which may further enhance comfort.25,26 The near-silent operation of nonpulsatile technology also makes these pumps less intrusive for patients and their caregivers, particularly in quiet public places.

**Evolving Pump Complications**

All MCS devices are subject to complications resulting from the complex interplay between pump and patient. Although device durability has been dramatically enhanced with continuous-flow pumps, stroke and infection remain substantial risks, and unanticipated hazards specific to rotary VADs have been recognized. The greatest recent impact of pump design on reducing adverse events is the extended durability of continuous-flow rotary pumps. Mechanical failure of first-generation electric and pneumatically driven pulsatile pumps frequently resulted in reoperation for device exchange or even death. In REMATCH, 35% of HM XVE recipients experienced component failure within 24 months.27 Similarly, in the HM II DT study, 20 of 59 patients randomly assigned to HM XVE required 21 device replacements and 2 device explants because of bearing wear and valve dysfunction.18 By contrast, current continuous-flow LVADs like the HM II are designed with only a single, nearly frictionless moving part (the impeller) and do not have a pusher plate or artificial valves. In the pivotal HM II DT trial, the rate of pump replacement was only 0.06/patient-year for HM II in comparison with 0.51/patient-year for HM XVE (P < 0.001). Reoperation to repair or replace the pump, a key secondary end point in the HM II DT trial, was significantly lower for the rotary pump (hazard ratio 0.18, P < 0.001). Continuous rotor activity ensures unidirectional blood flow and obviates the need for valved conduits, which were subject to structural valve deterioration. Primary pump failure remains exceedingly rare with the HM II, but device exchange may still be required for pump thrombosis, cannula malposition, or deep infection. In the HM II BTT experience of 133 implants, 1 device-related death and 5 pump replacements (VAD thrombosis in 2 patients, surgical complications in 3) were observed.28 Third-generation pumps currently under development operate without bearings by use of either hydrodynamically (eg, HVAD) or magnetically (DuraHeart LVAD, HeartMate III) levitated rotors, which may allow even greater pump longevity.29

Although LVAD durability has been greatly extended, the inherent risks of bleeding, stroke, and infection remain. Debilitating stroke is the most dreaded complication of MCS and is equally common with continuous-flow pumps and pulsatile devices. In the postmarketing BTT HM II study, stroke rate was 0.08 events/patient-year for HM II and 0.11 events/patient-year for the contemporaneous pulsatile devices, including HM XVE and Thoratec IVAD (P = 0.38).21 Embolic strokes appear more common than hemorrhagic strokes with all device designs,21 and may arise not only from in situ clot formation on a pump component, but also from...
ingested thrombus propelled through the device. In the randomized HM II DT trial, which enrolled sicker patients, disabling stroke was not statistically different between continuous and pulsatile flow (11% versus 12%, \( P=0.56 \)).\(^{15}\) Overall stroke rates were modestly lower with HM II compared to HM XVE (0.13 versus 0.22 events/patient-year, \( P=0.21 \)), with patients at equivalent risk of ischemic and hemorrhagic stroke. The ischemic stroke rate for HM II patients may not be significantly different from patients with end-stage heart failure without device support, although controlled comparative data do not exist. Data from the nonrandomized HeartWare HVAD BTT experience revealed similar risk of stroke in comparison with other VADs, with 0.10 ischemic and 0.05 hemorrhagic strokes/patient-year, and an overall risk of disabling stroke of 0.06 events/patient-year.\(^{30}\) Long-term stroke risk with the HVAD pump will be clarified with the extended enrollment phase of the Evaluation of the HeartWare Ventricle Assist Device for the Treatment of Advanced Heart Failure (ADVANCE) trial. Anticoagulation regimens may ultimately be device specific, and the relatively low-level anticoagulation recommended for the HM II may be inadequate for the HVAD. Stroke risk with the Jarvik 2000 has not been published.

The optimum level of antiplatelet and anticoagulant therapy to minimize both thromboembolic and hemorrhagic stroke is unknown, and few comparative data exist. The HM II has relatively low thrombotic risk provided patients are on an anticoagulation regimen that features an antiplatelet agent such as aspirin along with warfarin with an international normalized ratio goal of 1.5 to 2.0.\(^{22,31}\) As LVAD use expands into older patient populations, it must be remembered that advanced age remains the most potent risk factor for stroke. Indeed, stroke has become such a crucial safety endpoint that stroke-free survival will be used as the primary endpoint for the Evaluation of the HeartWare Ventricle Assist System for Destination Therapy of Advanced Heart Failure (ENDURANCE) clinical trial, the ongoing randomized study of the HVAD compared with contemporary continuous-flow pumps for DT.\(^{32}\) Careful adjudication of neurological events is now central to MCS trial design. Stroke risk may be particularly relevant for those patients intended as BTT because disabling stroke may render them ineligible for transplant. Stroke risk should be part of counseling before elective MCS, particularly as extended or lifetime mechanical support becomes increasingly common and stroke risk may not abate with time.

Device-related infection also remains common with MCS and has been described as the Achilles heel of circulatory assist.\(^{13}\) The majority of infections involve the percutaneous driveline, pump pocket, or both. Rotary blood pumps with smaller surface areas and thinner drivelines may be less prone to infection than pulsatile pumps. Pump design, patient selection, surgical technique, and driveline care appear to be the primary determinants of infectious risk.\(^{34}\) Immobilization of the driveline may help avoid torsion and breakdown of the cutaneous junction, the most common entry point for infections. Transcutaneous energy transfer systems may one day eliminate the need for a percutaneous driveline, although progress has been hampered by high-power requirements that outstrip current battery technology.\(^{35}\) Fortunately, infection involving the blood surface interface of the pump, known as pump endocarditis, is rare. Pump infections have dire consequences because they are so difficult to eradicate. Device-related infection even allows upgrade to United Network for Organ Sharing status IA. For those ineligible for transplant, device infection represents an incurable and often fatal complication of MCS.

Multiple distinct and largely unanticipated complications of continuous (or nonpulsatile) blood flow have emerged that were not experienced with pulsatile pumps. Continuous-flow VADs have been associated with bleeding from cerebral and gastrointestinal arteriovenous malformations.\(^{36,37}\) In addition to stimulating the formation of arteriovenous malformations, continuous axial flow produces high-shear stress that disrupts circulating high-molecular-weight multimers of von Willebrand factor, leading to an acquired von Willebrand syndrome with defective platelet aggregation.\(^{38,39}\) Mucosal bleeding risk is compounded by the requirement for anticoagulation. In addition, chronic aortic insufficiency may develop with prolonged continuous flow and can represent either an exacerbation of mild preexisting regurgitation or de novo insufficiency.\(^{23,40}\) Development of aortic insufficiency has been attributed to expansion of the aortic sinus, infrequent valve opening, and greater aortic diastolic pressures, each of which can contribute to leaflet fusion and valvular incompetence.\(^{41}\) The cumulative risk of stroke, infection, bleeding, and aortic insufficiency will shape the debate about the eventual cost-effectiveness of rotary LVADs for chronic heart failure.

Future Prospects for Pulsatile Flow, Biventricular Therapies, and Partial Support

Despite the ascendancy of continuous-flow pumps, pulsatile platforms still have an important role in the modern era. In acute cardiogenic shock, pulsatile flow maximizes both perfusion pressure and unloading of the pulmonary circuit and right heart.\(^{42}\) Pulsatile technology also has an exclusive role in the BTT setting when biventricular support or replacement is required, either in the form of biventricular assist devices or TAH. Pulsatile devices also allow for easier conversion from an LVAD to biventricular support with a single platform should right ventricular failure develop. Nevertheless, continuous-flow configurations for biventricular assist devices are being actively explored, and case reports of successful biventricular HM II and HVAD support have been published.\(^{43,44}\)

The TAH offers full circulatory replacement therapy for patients with irreversible biventricular failure, although only 2% to 3% of current MCS implants are TAHs.\(^{13}\) The pneumatically driven SynCardia TAH was FDA approved for BTT in 2004, and received Centers for Medicare and Medicaid Services coverage in 2008. It requires no surgical pocket, can provide up to 10 L/min flow with physiological control through both pulsatile pumping chambers, and has the shortest blood path of any circulatory device. However, the TAH requires adequate mediastinal space to accommodate the dual-chambered pump, and its utility has been limited by a large controller requiring permanent hospitalization.\(^{45}\) Syn-
Cardia’s next-generation portable pneumatic controller (Freedom Driver) is small enough at 5.9 kg that patients can be discharged from the hospital and remain relatively independent despite orthotopic mechanical replacement. The Freedom Driver is undergoing investigational device exemption investigation with the previously approved TAH as a BTT.56 Perhaps most importantly, the TAH is currently the only MCS option for transplant candidates with restrictive or infiltrative cardiomyopathies with ventricular cavities too small to accommodate apical inflow cannulae. Such patients were previously relegated to prolonged hospitalization on inotropes, and now they too have an MCS option that could allow discharge from the hospital while awaiting transplant. Device malfunction, along with bleeding, stroke, and infection, remain concerns with TAH technology.

Another important trend in pump development has been miniaturization, even at the expense of flow rate. Implantable miniature pumps may be able to deliver long-term partial circulatory support to allow recovery of ventricular function after an acute insult or provide durable assistance. The CircuLite Synergy micropump, under investigation, can provide up to 3 L/min of flow from the left atrium into the subclavian artery and can be implanted without cardiopulmonary bypass via a minithoracotomy.47 Investigators have also described using the continuity between the posterior aortic wall and left atrium as another means of providing LV support without entering the ventricle.48 As surgery becomes less invasive and successful strategies for long-term percutaneous support are realized, MCS implantation will likely become more proactive and move into less sick patients with earlier stage heart failure.

Changing Patient Populations

As pump design has evolved, so has the population of patients with advanced heart failure receiving MCS. With the recent expansion in use of the HM II for DT, there is now a meaningful cohort of patients receiving lifetime LVAD support. The success of LVAD therapy has generated debate about the degree of heart failure that should prompt implant and has altered decisions about listing for transplantation. Elements of the preimplant assessment have also been reconsidered, such as right ventricular (RV) function, nutritional status and age. LVAD programs have in turn evolved to meet the needs of the ever-expanding and varying group of patients living with MCS.

Evolving Role for LVADs and Transplantation

Since 1999, more than a third of all listed adult heart transplant candidates and 75% of those initially listed as United Network for Organ Sharing status IA have received MCS.49 Implantation of an LVAD in status I patients allows them to undergo transplantation relieved of the burden of chronic congestion, with improved end-organ function and nutritional status. Although United Network for Organ Sharing status I was originally conceived for patients with less than a week to live, the average waiting time in status I is now >6 months, during which patients with end-stage heart failure are exposed to risks of infection, blood clots, and pressure ulcers, and experience exhaustion of family support. In this era of prolonged waitlist times, LVAD therapy can allow patients to return home with an improved quality of life while waiting for a donor organ to become available.50 Early referral for device therapy may also be reasonable in patients listed for transplant who are anticipated to have a long waiting time because of blood type, large body size, or a high degree of allosensitization.

For patients listed as United Network for Organ Sharing status II, survival without transplant or LVAD has been improving, with 81% 1-year and 74% 2-year survival in the era between 2000 and 2005.51 Improved outcomes while listed may reflect better medical therapies or earlier listing (eg, lead-time bias) and have occurred despite older age and a greater burden of comorbidities. Survival with heart failure while listed as status II is similar to that with the current second-generation continuous-flow LVADs. However, mechanical support may offer improved functional capacity and quality of life in comparison with optimal medical therapy, including home inotropes. With limited donor organ availability, only 14% of all heart transplants in 2009 occurred in status II patients, highlighting the potential for expanded LVAD use.49 Because of the success of LVAD therapy, transplant without MCS may be best reserved for patients with dominant RV dysfunction, structural obstacles to isolated left ventricular support, or unacceptably high risk for reoperation. With extended LVAD durability, the eventual goal may be to avoid transplant and its attendant complications for as long as possible. This will likely require a change in patient, family, and/or provider expectations before VAD implantation.

LVADs have also been deployed as a bridge to candidacy in patients with potentially reversible or relative contraindications to transplant. Encouraging data exist for the reversal of secondary pulmonary hypertension in select patients, although, in many cases, RV dysfunction may persist even with LVAD support.52–55 If pulmonary vascular resistance remains elevated, sildenafil may be considered.56 Other contraindications to transplant such as severe chronic kidney disease or morbid obesity seldom improve to a degree that allows listing. Given the scarcity of donor organs and improving outcomes with LVAD support, recipients who are not transplant candidates at time of implant should be prepared for the possibility of lifetime mechanical support.

Earlier Timing for Durable Support

The INTERMACS profiles have been developed to define clinically important differences in the severity of disease among patients with advanced heart failure (Table 4).57 Nearly 70% of all registered VADs have been implanted in the sickest subset of patients with heart failure, those with critical cardiogenic shock (INTERMACS level 1) or progressive end-organ dysfunction despite inotropic support (INTERMACS level 2). Worsening INTERMACS profile has been consistently associated with higher perioperative mortality.58 In the past 2 years, the field has moved away from implanting primary LVADs in level 1 patients because of poor outcomes.59 Many are now receiving temporary percutaneous circulatory support, sometimes referred to as bridge to bridge, as a way to support circulation and triage the sickest patients for eventual durable LVAD. Waiting for end-organ failure or even more subtle signs of deblitation...
before moving to LVAD support is no longer acceptable.59 Similarly, destination LVAD should be considered an elective procedure in medically stable candidates rather than a bailout for the patient sliding into refractory low-output heart failure despite inotropic or temporary circulatory support. Some patients may require an inpatient medical tune-up with vasoactive or diuretic therapy immediately before LVAD surgery.

Dependence on intravenous positive inotropes has traditionally been considered the threshold that prompts consideration of advanced therapies. Patients with advanced systolic heart failure, however, are currently eligible for destination LVAD coverage even if they are not dependent on inotropes, provided they have symptoms at rest and a peak oxygen consumption <14 mL kg⁻¹ min⁻¹ on optimal oral therapies (INTERMACS levels 4 and 5) (Table 5). Only 18% of durable adult LVADs are currently implanted in patients not yet dependent on intravenous inotropes.13 Low implant rates in ambulatory heart failure may reflect reluctance of both physicians and patients. Ambulatory patients with advanced heart failure should have ongoing discussions about the trade-offs of living with heart failure in comparison with undergoing VAD operation to identify preferences and thresholds for considering elective LVAD therapy.60

Fortunately, the evidence base to guide LVAD use before inotrope dependence is growing. Equipoise now exists for the study of smaller, more reliable continuous-flow pumps for DT in “less sick” patient with advanced heart failure. The NIH has sponsored the Randomized Evaluation of VAD Intervention before Inotropic Therapy (REVIVE-IT) trial to study LVAD therapy in patients who have advanced heart failure with significant functional impairment and who are ineligible for transplant, but who have not yet manifested serious consequences of end-stage heart failure, such as severe end-organ dysfunction, immobility, or cardiac cachexia.61 The REVIVE-IT pilot study is in the advanced planning stages and will randomly assign 100 patients with moderately advanced heart failure in a 1:1 ratio to the HeartWare HVAD, an intrapericardially implanted continuous-flow centrifugal pump, or optimal medical therapy.62 The upcoming industry-sponsored ROADMAP (Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients) trial will be a prospective, nonrandomized observational study of NYHA III/IV patients not yet on inotropes that will compare the postmarketing effectiveness of the HM II for DT on optimal medical therapy. In addition, as part of the ongoing INTERMACS effort a parallel registry of medically managed chronic systolic heart failure patients with refractory NYHA class III or IV symptoms is being assembled as part of the Medical Arm of Mechanically Assisted Circulatory Support (MEDAMACS) initiative. This prospective, observational medical registry will have a particular focus on INTERMACS profiles 4 to 6 to help define the natural history of ambulatory advanced heart failure and refine patient selection in this crucial

<table>
<thead>
<tr>
<th>Level</th>
<th>Patient Characteristics</th>
<th>Implants* (1/2009–6/2010), %</th>
<th>Inotrope Dependent</th>
<th>Target for REVIVE-IT DT Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Critical cardiogenic shock despite escalating support</td>
<td>17</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>Progressive decline despite inotropes</td>
<td>45</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>Clinically stable, but inotrope dependent</td>
<td>20</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>Recurrent, not refractory, advanced heart failure</td>
<td>12</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>Exertion intolerant, but comfortable at rest and able to perform activities of daily living with slight difficulty</td>
<td>3</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>Exertion limited; able to perform mild activity, but fatigued within a few minutes of exertion</td>
<td>2</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>Advanced NYHA class III</td>
<td>1</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

INTERMACS indicates Interagency Registry of Mechanically Assisted Circulatory Support; NYHA, New York Heart Association; and REVIVE-IT, Randomized Evaluation of VAD Intervention before Inotropic Therapy.

*Data from Kirklin et al.13

Table 5. Requirements for Destination Therapy Coverage

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device</td>
<td>FDA-approved device for DT (HeartMate XVE, HeartMate II)</td>
</tr>
<tr>
<td>Patient</td>
<td>Chronic NYHA class IV heart failure</td>
</tr>
<tr>
<td></td>
<td>Not a candidate for heart transplant</td>
</tr>
<tr>
<td></td>
<td>Did not respond to optimal medical management for 45 of last 60 d (including β-blockers and ACE inhibitors if tolerated), or IABP for 7 d, or IV inotrope for 14 d</td>
</tr>
<tr>
<td></td>
<td>LVEF ≤25%, and severe functional limitation with peak VO₂ &lt;14 mL kg⁻¹ min⁻¹, unless on IABP or inotropes, or physically unable to complete test</td>
</tr>
<tr>
<td>Facility</td>
<td>Experienced surgeon (≥10 VAD/TAH implants in 36 mo)</td>
</tr>
<tr>
<td></td>
<td>Member of INTERMACS Registry</td>
</tr>
<tr>
<td></td>
<td>Joint Commission-certified VAD program</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; DT, destination therapy; IABP, intra aortic balloon pump; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; IV, intravenous; NYHA, New York Heart Association; TAH, total artificial heart; VAD, ventricular assist device; and VO₂, oxygen consumption.

spectrum of disease where the greatest expansion in LVAD use is anticipated.

### Triggers for Evaluation of MCS Candidacy

The clinical signposts that mark a downward trajectory of patients with chronic heart failure, and that may serve as triggers for referral for MCS, are often missed or recognized only in retrospect (Table 6). Common indicators of increased mortality in heart failure include two or more hospitalizations for acute decompensation in a 12-month period, development of a circulatory or renal limitation to angiotensin-converting enzyme inhibitor therapy, hypotension in response to β-blocker therapy, a peak oxygen consumption <14 to 16 mL · kg⁻¹ · min⁻¹ or <50% predicted, symptoms at rest (NYHA class IV) on most days, Six-minute walk distance <300 m, Persistent hyponatremia (serum sodium <134 mEq/L), Recurrent, refractory ventricular tachyarrhythmias, Cardiac cachexia.

ACE indicates angiotensin-converting enzyme; HF, heart failure; NYHA, New York Heart Association; and V0₂, oxygen consumption.

**Table 6. Triggers for Referral for VAD Evaluation**

<table>
<thead>
<tr>
<th>Trigger</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inability to wean inotropes or frequent inotrope use</td>
<td></td>
</tr>
<tr>
<td>Peak V0₂ &lt;14–16 mL · kg⁻¹ · min⁻¹ or &lt;50% predicted</td>
<td></td>
</tr>
<tr>
<td>Two or more HF admissions in 12 mo</td>
<td></td>
</tr>
<tr>
<td>Worsening right heart failure and secondary pulmonary hypertension</td>
<td></td>
</tr>
<tr>
<td>Diuretic refractoriness associated with worsening renal function</td>
<td></td>
</tr>
<tr>
<td>Circulatory-renal limitation to ACE inhibition</td>
<td></td>
</tr>
<tr>
<td>Hypotension limiting β-blocker therapy</td>
<td></td>
</tr>
<tr>
<td>NYHA class IV symptoms at rest on most days</td>
<td></td>
</tr>
<tr>
<td>Seattle HF model score with anticipated mortality &gt;15% at 1 y</td>
<td></td>
</tr>
<tr>
<td>Six-minute walk distance &lt;300 m</td>
<td></td>
</tr>
<tr>
<td>Persistent hyponatremia (serum sodium &lt;134 mEq/L)</td>
<td></td>
</tr>
<tr>
<td>Recurrent, refractory ventricular tachyarrhythmias</td>
<td></td>
</tr>
<tr>
<td>Cardiac cachexia</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 2.** Decision tree for elective mechanical circulatory support in advanced heart failure. This is a suggested algorithm for decision making about elective mechanical circulatory support in advanced heart failure. Once a trigger for VAD evaluation has been identified, patients should be referred to an experienced MCS center where all advanced therapies, including transplant and VAD, can be considered. Decisions about MCS are contingent on eligibility for transplantation, and the likelihood of RV failure after LVAD implant, as well. Consideration for a candidate for medical therapy alone and may benefit from early referral to supportive cardiology. AKI indicates acute kidney injury; BIVAD, biventricular assist device; BTT, bridge to transplant; DT, destination therapy; LVAD, left ventricular assist device; MCS, mechanical circulatory support; RV, right ventricular; and TAH, total artificial heart.

Evolving Preimplant Considerations

Considerable effort has gone into developing risk scores to predict perioperative outcomes after LVAD implant. Risk factors for perioperative mortality focus on indices of hepatic and renal dysfunction and poor nutrition, which may be manifestations of right heart failure that are unaddressed by left-sided support alone.70,71 Risk scores developed in the pulsatile flow era may be less discriminating when applied to continuous-flow devices, in part, because of improved outcomes.72 The latest HM II risk score showed that multivariabile preoperative predictors of mortality included older age, higher creatinine, low albumin, and implant center inexperience.71 Right heart failure after LVAD implant results in up to a 6-fold increase risk of death and is a major contributing factor in prolonged hospitalizations.73 Accurate assessment of RV function is required before LVAD implant, particularly when transplant is not an option, because biventricular support is not yet feasible (or approved) for DT. RV dysfunction and cardiac cachexia. Ventricular tachycardia refractory to medical and ablative therapies, even in the absence of severe heart failure, is also an indication for considering MCS support.

The Seattle Heart Failure Model has been applied broadly to estimate mortality and anticipate benefits from medical or device therapies.66 This model also predicts mortality after LVAD implant, although it may underestimate the risk of VAD or urgent transplant listing among ambulatory patients.67,68 Patients with anticipated mortality >15% at 1 year or >20% at 2 years based on the Seattle Heart Failure Model should be considered high risk and evaluated for MCS candidacy. For patients not facing imminent death, but who have severe symptom burden, the functional benefits alone may justify referral for LVAD therapy. The HM II has been shown to increase 6-minute walk distance >200 m, with most patients improving to NYHA class I or II.69 Patients approaching any of these signposts should be considered for referral to an advanced heart disease program to determine candidacy for transplant, MCS, or both (Figure 2).
tion present with inotropic support before LVAD appears to persist after implant, with uncertain long-term consequences. The multitude of multiple LV clinical risk scores has been developed to anticipate RV failure and plan for biventricular support (Table 7). However, none of these scores was derived in a DT cohort or with newer continuous-flow LVADs, which may be even more sensitive to RV failure because of greater systemic venous return and exaggerated interventricular dependence.

Proactive relief of congestion in the hospital, often guided by a pulmonary artery catheter, is indicated to prepare the patient for implant. Early postoperative use of inotropes or inhaled pulmonary vasodilators, or proactive right ventricular assist device placement may allow the best chance for recovery of RV function. The ability to adjust continuous pump speed in real time under echocardiographic guidance may also help optimize RV contractile geometry and minimize residual tricuspid regurgitation. Although some surgeons advocate prophylactic tricuspid valvuloplasty, other surgeons have shown no benefit. Selection of patients for isolated LVAD will also be informed by our improved understanding of load-independent RV function (eg, RV stroke work index), pulmonary impedance, and RV contractile reserve. The right heart is central to all decisions surrounding LVAD therapy.

Adequate nutritional support reduces the risk of postoperative infection and improves functional recovery after LVAD placement. Yet patients with end-stage heart failure have profound metabolic imbalances, particularly when hepatic and gastrointestinal congestion is a prominent presenting feature. Patients with cachexia and a low prealbumin and/or elevated C-reactive protein are at particularly high risk for perioperative death, often from infection. Other markers of poor nutritional status include reduced levels of serum albumin, total protein, total cholesterol, and lymphocyte count. Aggressive nutritional support, including enteral feeding, should be considered in all LVAD candidates with any sign of low nutritional reserve. In contrast to its role in transplant listing, obesity is not a contraindication to LVAD implantation, nor does it appear to increase the risk of driveline infection as previously feared. Low body mass index has consistently been shown to be a greater predictor of mortality after LVAD than elevated body mass index. Whereas LVAD therapy has been proposed in BTC patients to facilitate weight reduction, there are few data to support a bridge to weight loss strategy, and such patients should be prepared for the possibility of lifelong LVAD support.

Age is also one of the most commonly cited reasons for transplant ineligibility, making older patients a target population for expanded LVAD use. Nearly 75% of patients with heart failure are >65 years of age, and the average age of patients hospitalized in the United States with low ejection fraction heart failure is 75 years. The interaction between age and LVAD outcomes is evolving. In the INTERMACS registry, age has been consistently associated with an increased hazard of early and late mortality, although the global improvements in results with continuous-flow pumps may diminish the relative impact of age on outcomes. Indices of frailty, which may be independent of age, may be even more potent predictors of outcome after cardiac surgery. Advancing age tracks with greater prevalence of comorbidities such as chronic kidney disease, diabetes mellitus, and cerebrovascular disease, which may be greater drivers of adverse outcomes. Improvement in survival and quality of life after HM II therapy in select patients >70 years, including those self-referred from hospice, may not be different from younger recipients, suggesting that age should not be used as an independent contraindication to LVAD therapy at experienced centers.

**Evolution of MCS Programs**

Use of LVAD therapy is best accomplished within an integrated program of advanced heart disease care. Successful programs emphasize teamwork and offer optimization of medical and device therapies, evaluation for transplant candidacy and MCS, and, when appropriate, a focus on palliative care and end-of-life choices. A full menu of MCS options should be available, from temporary percutaneous support to the latest durable LVAD or biventricular assist technology, so that device selection can be tailored to patient circumstances. Center experience and procedural volume are of critical importance given the complexity of patient care with LVADs. Certification of a destination LVAD program requires not only heart failure cardiologists and cardiac

![Table 7. Predictors of Right Ventricular Failure after VAD Implantation](https://example.com/table7)

<table>
<thead>
<tr>
<th>Definition of RV Failure</th>
<th>Predictors</th>
<th>Matthews et al73</th>
<th>Fitzpatrick et al74</th>
<th>Drakos et al75</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVAD or ECMO</td>
<td>Vasopressor requirement</td>
<td>Inhaled NO ≥48 h</td>
<td>Cardiac index &lt;2.2 L ( \cdot ) ( \cdot ) ( \cdot ) m⁻¹ ( \cdot ) min⁻¹ ( \cdot ) m⁻²</td>
<td>Inhaled NO ≥48 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inotrope ≥14 d</td>
<td>RV stroke work index &lt;0.25</td>
<td>Inotrope ≥14 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Home inotrope</td>
<td>Severe RV dysfunction on echo</td>
<td>Elevated PVR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total bilirubin ≥2 mg/dL</td>
<td>Creatinine &gt;1.9 mg/dL</td>
<td>Preoperative IABP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Creatinine &gt;2.3 mg/dL</td>
<td>Previous cardiac surgery</td>
<td>Destination therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Systolic BP &lt;95 mm Hg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AST indicates aspartate aminotransferase; BP, blood pressure; ECMO, extracorporeal membrane oxygenation; IABP, intraaortic balloon pump; NO, nitric oxide; PVR, pulmonary vascular resistance; RV, right ventricle; and RVAD, right ventricular assist device.
surgeons, but also committed providers from cardiovascular imaging, nursing, psychiatry, social work, physical therapy, nutrition, and financial counseling. In addition, subspecialists in infectious disease, gastroenterology, and nephrology with a focus on LVAD care are critical to anticipating and managing device-related complications. Quality assessment and performance initiatives, along with frequent financial review, further enhance program growth and development.

LVAD patients and their families require intensive education before implant and dedicated postoperative management to prepare them for life outside the hospital. Patients and their caregivers must master device alarm troubleshooting, battery changes, and driveline care. In addition, local first responders must be trained and power companies notified to ensure access to back-up generators. Committed LVAD care does not end with hospital discharge. Much of the responsibility for this rests on the shoulders of dedicated VAD coordinators, each of whom is responsible for 15 or more patients with LVADs. Routine outpatient encounters with LVAD patients focus on blood pressure and volume control, meticulous driveline care, anticoagulation adjustment, and counseling to facilitate reintegration into the community and prevent caregiver burnout. Comprehensive, multidisciplinary outpatient MCS clinics have evolved to address these varied needs. Institutional commitment to MCS program excellence is required to sustain the promising outcomes achieved thus far with LVAD therapy.

Conclusions

The rapid progress of MCS technology in recent years has extended survival and improved quality of life for select patients with advanced heart failure. Indeed, mechanical support has become central to the evidence-based care of chronic, refractory heart failure. For the first time, there is a meaningful option for lifelong support even in patients who are not candidates for transplantation. Novel pump design has improved clinical outcomes, altered the profile of MCS candidates, and changed the structure of advanced heart disease programs. With these advances have come new challenges and opportunities. This article represents the first in a series of invited reviews on Advances in Mechanical Circulatory Support to appear in Circulation. Future articles will address percutaneous circulatory support to treat cardiogenic shock, imaging of ventricular function and myocardial recovery, bleeding and thrombosis risk with continuous flow, lessons from registry data, bridge to myocardial recovery, quality of life on MCS, and the cost-effectiveness of VADs in advanced heart failure.

Disclosures

None.

References


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74. Matthews JC, Koelling TM, Pagani FD, Aaronson KD. The right ventricular failure risk score a pre-operative tool for assessing the risk of right ventricular failure in left ventricular assist device candidates. J Am Coll Cardiol. 2008;51:2163–2172.


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