Implantable Ventricular Assist Devices and Total Artificial Hearts

I. Description

A ventricular assist device (VAD) is a mechanical support attached to the native heart and vessels to augment cardiac output. The total artificial heart (TAH) replaces the native ventricles and is attached to the pulmonary artery and aorta; the native heart is typically removed. Both the VAD and TAH may be used as a bridge to heart transplantation or as destination therapy in those not candidates for transplantation. The VAD has also been used as a bridge to recovery in patients with reversible conditions affecting cardiac output.

Ventricular Assist Device
For individuals who have end-stage heart failure who receive a VAD as a bridge to transplant, the evidence includes single-arm trials and observational studies. Relevant outcomes are overall survival, symptoms, functional outcomes, quality of life (QOL), and treatment-related mortality and morbidity. There is a substantial body of evidence from clinical trials and observational studies supporting implantable VADs as a bridge to transplant in patients with end-stage heart failure, possibly improving mortality as well as QOL. These studies have reported that substantial numbers of patients have survived to transplant in situations in which survival would not be otherwise expected. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have end-stage heart failure who receive a VAD as destination therapy, the evidence includes a trial and multiple single-arm studies. Relevant outcomes are overall survival, symptoms, functional outcomes, QOL, and treatment-related mortality and morbidity. A well-designed trial, with 2 years of follow-up data, has demonstrated an advantage of implantable VADS as destination therapy for patients ineligible for heart transplant. Despite an increase in adverse events, both mortality and QOL appear to be improved for these patients. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.
Total Artificial Heart
For individuals who have end-stage heart failure who receive a TAH as a bridge to transplant, the evidence includes case series. Relevant outcomes are overall survival, symptoms, functional outcomes, QOL, and treatment-related mortality and morbidity. Compared with VADs, the evidence for TAHs in these settings is less robust. However, based on the lack of medical or surgical options for these patients and the evidence case series provide, TAH is likely to improve outcomes for a carefully selected population with endstage biventricular heart failure awaiting transplant who are not appropriate candidates for a left VAD. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have end-stage heart failure who receive a TAH as destination therapy, the evidence includes 2 case series. Relevant outcomes are overall survival, symptoms, functional outcomes, QOL, and treatment-related mortality and morbidity. The body of evidence for TAHs as destination therapy is too limited to draw conclusions. The evidence is insufficient to determine the effects of the technology on health outcomes.

Percutaneous Ventricular Assist Device
For individuals with cardiogenic shock or who undergo high-risk cardiac procedures who receive a percutaneous VAD (pVAD), the evidence includes randomized controlled trials. Relevant outcomes are overall survival, symptoms, morbid events, functional outcomes, QOL, and treatment-related mortality and morbidity. Four randomized controlled trials of pVAD vs intra-aortic balloon pump (IABP) for patients in cardiogenic shock failed to demonstrate a mortality benefit and reported higher complication rates associated with pVAD use. Another randomized controlled trial comparing pVAD with IABP as an adjunct to high-risk percutaneous coronary interventions was terminated early due to futility; analysis of enrolled subjects did not demonstrate significant improvements in the pVAD group. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with cardiogenic shock refractory to IABP who receive a pVAD, the evidence includes case series. Relevant outcomes are overall survival, symptoms, morbid events, functional outcomes, QOL, and treatment-related mortality and morbidity. Case series of patients with cardiogenic shock refractory to IABP have reported improved hemodynamic parameters following pVAD placement. However, these uncontrolled series does not provide evidence that pVADs improve mortality, and high rates of complications have been reported with pVAD use. The evidence is insufficient to determine the effects of the technology on health outcomes.

II. Background

HEART FAILURE
Heart failure may be the consequence of a number of differing etiologies, including ischemic heart disease, cardiomyopathy, congenital heart defects, or rejection of a heart transplant. The reduction of cardiac output is considered to be severe when systemic circulation cannot meet the body’s
needs under minimal exertion. Heart transplantation improves quality of life and has survival rates at 1, 5, and 10 years of 88%, 74%, and 55%, respectively. The number of candidates for transplants exceeds supply of donor organs; thus the interest in the development of mechanical devices.

Treatment

**Total Artificial Hearts**

Initial research into mechanical assistance for the heart focused on the total artificial heart (TAH), a biventricular device that completely replaces the function of the diseased heart. An internal battery required frequent recharging from an external power source. Many systems use a percutaneous power line, but a transcutaneous power-transfer coil allows for a system without lines traversing the skin, possibly reducing the risk of infection. Because the heart must be removed, failure of the device is synonymous with cardiac death.

A fully bioprosthetic TAH, which is fully implanted in the pericardial sac and is electrohydraulically actuated, has been developed and tested in 2 patients but is currently experimental.

**Ventricular Assist Devices**

Implantable ventricular assist devices (VADs) are attached to the native heart, which may have enough residual capacity to withstand a device failure in the short term. In reversible heart failure conditions, the native heart may regain some function, and weaning and explanting of the mechanical support system after months of use has been described. VADs can be classified as internal or external, electrically or pneumatically powered, and pulsatile or continuous-flow. Initial devices were pulsatile, mimicking the action of a beating heart. More recent devices may utilize a pump, which provides continuous flow. Continuous devices may move blood in rotary or axial flow.

At least 1 VAD system developed is miniaturized and generates an artificial pulse, the HeartMate 3 Left Ventricular Assist System.

Surgically-implanted VADs represent a method of providing mechanical circulatory support for patients not expected to survive until a donor heart becomes available for transplant or for whom transplantation is contraindicated or unavailable. VADs are most commonly used to support the left ventricle, but right ventricular and biventricular devices may be used. The device is larger than most native hearts, and therefore the size of the patient is an important consideration; the pump may be implanted in the thorax or abdomen or remain external to the body. Inflow to the device is attached to the apex of the failed ventricle, while outflow is attached to the corresponding great artery (aorta for left ventricle, pulmonary artery for right ventricle). A small portion of ventricular wall is removed for insertion of the outflow tube; extensive cardiotomy affecting the ventricular wall may preclude VAD use.

**Percutaneous VADs**

Devices in which the majority of the system’s components are external to the body are for short-term use (6 hours to 14 days) only, due to the increased risk of infection and need for careful, in-
hospital monitoring. Some circulatory assist devices are placed percutaneously, (i.e., are not implanted). They may be referred to as percutaneous VADs (pVADs). A pVAD is placed through the femoral artery. Two different pVADs have been developed, the TandemHeart and the Impella device. In the TandemHeart system, a catheter is introduced through the femoral vein and passed into the left atrium via transseptal puncture. Oxygenated blood is then pumped from the left atrium into the arterial system via the femoral artery. The Impella device is also introduced through a femoral artery catheter. In this device, a small pump is contained within the catheter placed into the left ventricle. Blood is pumped from the left ventricle, through the device, and into the ascending aorta. Adverse events associated with pVAD include access-site complications such as bleeding, aneurysms, or leg ischemia. Cardiovascular complications can also occur, such as perforation, myocardial infarction, stroke, and arrhythmias.

There are several situations in which pVADs may be beneficial: (1) cardiogenic shock that is refractory to medications and intra-aortic balloon pump, (2) cardiogenic shock as an alternative to intra-aortic balloon pump, and (3) invasive cardiac procedures in high-risk patients who need circulatory support.

Intra-aortic balloon pumps are outside the scope of this evidence review.

**REGULATORY STATUS**

A number of mechanical circulatory support devices have been approved or cleared for marketing by U.S. Food and Drug Administration (FDA). These devices are summarized in Table 1 and discussed in the following sections.

**Table 1. Available Mechanical Circulatory Support Devices**

<table>
<thead>
<tr>
<th>Device</th>
<th>Manufacturer</th>
<th>Date of Initial Approval</th>
<th>Method of FDA Clearance</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>VADs</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Thoratec IVAD</td>
<td>Thoratec</td>
<td>August 2004</td>
<td>PMA Supplement</td>
<td>Bridge to transplant and postcardiotomy</td>
</tr>
<tr>
<td>DeBakey VAD Child</td>
<td>MicroMed</td>
<td>February 2004</td>
<td>HDE</td>
<td>Bridge to Transplant in children 5–16 years of age</td>
</tr>
<tr>
<td>HeartMate II</td>
<td>Thoratec</td>
<td>April 2008</td>
<td>PMA</td>
<td>Bridge to transplant and destination</td>
</tr>
<tr>
<td>Centrimag (now Thoratec)</td>
<td>Levitronix</td>
<td>October 2008</td>
<td>HDE</td>
<td>Postcardiotomy</td>
</tr>
</tbody>
</table>
In October 2004, the temporary CardioWest Total Artificial Heart (SynCardia Systems, Tuscon, AZ) was approved by the FDA through the premarket approval (PMA) process for use as a bridge to transplant in cardiac transplant-eligible candidates at risk of imminent death from biventricular failure. This device is also intended for use inside the hospital. In April 2010, FDA approved a name change to SynCardia Temporary Total Artificial Heart. FDA product code: LOZ.

In September 2006, the AbioCor Implantable Replacement Heart System (Abiomed, Danvers, MA) was approved by FDA through the humanitarian device exemption (HDE) process for use in severe biventricular end-stage heart disease patients who are not cardiac transplant candidates and who:

- are younger than 75 years of age;
- require multiple inotropic support;
- are not treatable by left VAD destination therapy; and
- are not weanable from biventricular support if on such support.

In addition to meeting other criteria, patients who are candidates for the AbioCor TAH must undergo a screening process to determine if their chest volume is large enough to hold the device. The device is too large for approximately 90% of women and for many men. FDA HDE: H040006.

**Ventricular Assist Devices**

In December 1995, the Thoratec Ventricular Assist Device System (Thoratec Corp., Pleasanton, CA) was approved by FDA through the PMA process for use as a bridge to transplantation in patients suffering from end-stage heart failure. The patient should meet all of the following criteria:

- candidate for cardiac transplantation,
- imminent risk of dying before donor heart procurement, and
- dependence on, or incomplete response to, continuous vasopressor support.
In May 1998, supplemental approval for this device was given for the indication for postcardiotomy patients unable to be weaned from cardiopulmonary bypass. In June 2001, supplemental approval was given for a portable external driver to permit excursions within a 2-hour travel radius of the hospital when accompanied by a trained caregiver. In November 2003, supplemental approval was given to market the device as Thoratec Paracorporeal VAD. In August 2004, supplemental approval was given to a modified device to be marketed as the Thoratec Implantable VAD for the same indications. In January 2008, supplemental approval was given to rescind Paracorporeal VAD use.

In February 2004, the DeBakey VAD Child pump was approved by FDA through the HDE process for both home and hospital use for children between the ages of 5 and 16 years who have end-stage ventricular failure requiring temporary mechanical blood circulation until a heart transplant is performed.

In April 2008, continuous flow device HeartMate II LVAS device (Thoratec, Pleasanton, CA) was approved by FDA through the PMA process for use as a bridge to transplantation in cardiac transplant candidates at risk of imminent death from nonreversible left ventricular failure. The HeartMate II LVAS device is intended for use both inside and outside the hospital. In January 2010, the device received the added indication as destination therapy for use in patients with New York Heart Association Class IIIB or IV end-stage left ventricular failure who have received optimal medical therapy for at least 45 of the last 60 days and are not candidates for cardiac transplantation.

In October 2008, device CentriMag Right Ventricular Assist Device (Levitronix, Zurich) was approved by FDA under the HDE process to provide temporary circulatory support for up to 14 days for patients in cardiogenic shock due to acute right-sided heart failure.

In December 2011, the Berlin Heart EXCOR Pediatric VAD was approved by FDA under the HDE for pediatric patients with severe isolated left ventricular or biventricular dysfunction who are candidates for cardiac transplant and require circulatory support.

In December 2012, FDA approved the HeartWare Ventricular Assist System (HeartWare, Miami Lakes, FL) through the PMA process. The device is approved as a bridge to cardiac transplantation in patients at risk for death from refractory end-stage left ventricular heart failure.

FDA product code: DSQ

**Percutaneous VADs (Circulatory Assist Devices)**

In May 2008, the Impella Recover LP 2.5 Percutaneous Cardiac Support System (Abiomed, Aachen, Germany) was cleared for marketing by FDA through the 510(k) process for short-term (<6 hours) use in patients requiring circulatory support.
In March 2015, the Impella 2.5 System received approval through the PMA process for temporary ventricular support during high-risk percutaneous coronary interventions.

The TandemHeart (Cardiac Assist, Pittsburgh) received a similar 510(k) approval for short-term circulatory support in September 2005. FDA product code: KFM.

Several other devices are in clinical trials or awaiting FDA review.

III. Criteria/Guidelines

A. Bridge to Transplantation

1. Implantable ventricular assist devices (VADs) with Food and Drug Administration (FDA) approval or clearance are covered (subject to Limitations and Administrative Guidelines) as a bridge to heart transplantation for patients who are currently listed as heart transplantation candidates and not expected to survive until a donor heart can be obtained, or are undergoing evaluation to determine candidacy for heart transplantation.

2. Implantable VADs with FDA approval or clearance, including humanitarian device exemptions, are covered (subject to Limitations and Administrative Guidelines) as a bridge to heart transplantation in children 16 years old or younger who are currently listed as heart transplantation candidates and not expected to survive until a donor heart can be obtained, or are undergoing evaluation to determine candidacy for heart transplantation.

3. Total artificial hearts (TAHs) with FDA-approved devices are covered (subject to Limitations/Exclusions and Administrative Guidelines) as a bridge to heart transplantation for patients with biventricular failure meeting all of the following conditions:
   a. Who have no other reasonable medical or surgical treatment options
   b. Who are ineligible for other univentricular or biventricular support devices
   c. And are currently listed as heart transplantation candidates or are undergoing evaluation to determine candidacy for heart transplantation, and not expected to survive until a donor heart can be obtained.

B. Destination Therapy

Implantable VADs with FDA approval or clearance are covered (subject to Limitations and Administrative Guidelines) as destination therapy with end-stage heart failure patients who are ineligible for human heart transplant and who meet the following REMATCH study criteria:

1. New York Heart Association class IV heart failure for \( \geq 60 \) days, or
2. Patients in New York Heart Association class III or IV for 28 days, received \( \geq 14 \) days of support with intra-aortic balloon pump or dependent on intravenous inotropic agents, with 2 failed weaning attempts.
In addition, patients must not be candidates for human heart transplant for one or more of the following reasons:

a) Age > 65 years; or  
b) Insulin dependent diabetes with end-organ damage; or  
c) Chronic renal failure (serum creatinine > 2.5 mg/dL for ≥90 days); or  
d) Presence of other clinically significant condition.

C. Postcardiotomy Setting/Bridge to Recovery
Implantable VADs with FDA approval or clearance are covered (subject to Limitations and Administrative Guidelines) in the postcardiotomy setting in patients who are unable to be weaned off cardiopulmonary bypass.

D. For Medicare patients, see the NCD for Artificial Hearts and Related Devices (20.9) found on the CMS web site regarding eligibility requirements.

IV. Limitations/Exclusions

A. Removal of the device prior to transplantation (CPT codes 33977-33978) is considered part of the global fee and is incidental to the heart transplant.

B. Other applications of implantable ventricular devices or total artificial hearts are not covered, including but not limited to, the use of TAHs as destination therapy because it is not known to be effective in improving health outcomes.

C. The use of non-FDA approved or cleared implantable VADs or total artificial hearts are not covered.

D. Percutaneous VADs (pVAD) are not covered for all indications because they are not known to be effective in improving health outcomes.

V. Administrative Guidelines

A. Precertification is not required. HMSA reserves the right to perform retrospective review using the above criteria to validate if services rendered met payment determination criteria.

B. Applicable codes:

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>33975</td>
<td>Insertion of ventricular assist device; extracorporeal, single ventricle</td>
</tr>
<tr>
<td>33976</td>
<td>Extracorporeal, biventricular</td>
</tr>
<tr>
<td>33977</td>
<td>Removal of ventricular assist device; implantable extracorporeal, single ventricle</td>
</tr>
<tr>
<td>33978</td>
<td>Extracorporeal, biventricular</td>
</tr>
<tr>
<td>33979</td>
<td>Insertion of ventricular assist device; implantable intracorporeal, single ventricle</td>
</tr>
</tbody>
</table>
C. Codes that do not meet payment determination criteria:

<table>
<thead>
<tr>
<th>CPT</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>33990</td>
<td>Insertion of ventricular assist device, percutaneous including radiological supervision and interpretation; arterial access only</td>
</tr>
<tr>
<td>33991</td>
<td>;both arterial and venous access, with transseptal puncture</td>
</tr>
<tr>
<td>33992</td>
<td>Removal of percutaneous ventricular assist device at separate and distinct session from insertion</td>
</tr>
<tr>
<td>33993</td>
<td>Repositioning of percutaneous ventricular assist device with imaging guidance at separate and distinct session from insertion</td>
</tr>
</tbody>
</table>

VI. Scientific Background

This policy was created in November 1996 and has been regularly updated with searches of the MEDLINE database. The most recent literature review was performed for the period up to June 22, 2017.

This literature review focuses on 3 types of devices: (1) ventricular assist devices (VADs), (2) total artificial hearts (TAHs), and (3) percutaneous VADs (pVADs). This literature review addresses short-term use of the devices as a bridge to recovery or transplantation. Left VADs (LVADs) and TAHs are also evaluated as longer term destination therapies for patients who are not transplant candidates. The following is a summary of the key literature to date.

Assessment of efficacy for therapeutic intervention involves a determination of whether the intervention improves health outcomes. The optimal study design for this purpose is a randomized controlled trial (RCT) that includes clinically relevant measures of health outcomes. Intermediate outcome measures, also known as surrogate outcome measures, may also be adequate if there is an established link between the intermediate outcome and true health outcomes. Nonrandomized comparative studies and uncontrolled studies can sometimes provide useful information on health outcomes, but are prone to biases such as noncomparability of treatment groups, placebo effect, and variable natural history of the condition.

VENTRICULAR ASSIST DEVICES
**VADS as Bridge to Recovery**

VADs may have a role in bridging patients to recovery, particularly if there is reverse remodeling of the left ventricle.

In 2016, Acharya et al reported on patients who underwent VAD placement for acute myocardial infarction (AMI) who were enrolled in the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) registry, a prospective national registry of Food and Drug Administration (FDA)-approved durable mechanical circulatory support (MCS) devices. Patients who had an AMI as the admitting diagnosis or a major myocardial infarction (MI) as a hospital complication that resulted in VAD implantation (n=502) were compared with patients who underwent VAD implantation for non-AMI indications (n=9727). Patients in the AMI group were generally sicker at baseline, with higher rates of smoking, severe diabetes, and peripheral vascular disease, but had fewer cardiac surgeries and recent cardiovascular hospitalizations. Most AMI patients (53.8%) were implanted with a “bridge-to-candidacy” strategy. At 1 month post-VAD, 91.8% of the AMI group were alive with the device in place. At 1 year post-VAD, 52% of the AMI group were alive with the device in place, 25.7% had received a transplant, 1.6% had their VAD explanted for recovery, and 20.7% died with the device in place.

Two additional 2016 publications from the INTERMACS registry reported on cardiac recovery in patients implanted with LVADs. Wever-Pinzon et al (2016) included adults registered between March 2006 and June 2015 excluding those who had a right VAD only, TAH, or prior heart transplant (n=15,631). One hundred twenty-five of these patients had an a priori bridge to recovery LVAD strategy. Cardiac recovery occurred in 192 (1.3%) of the LVAD patients overall and in 14 (11.2%) of the bridge to recovery patients. Clinical characteristics associated with recovery were age less than 50 years, nonischemic cardiomyopathy, time from cardiac diagnosis less than 2 years, absence of implantable cardioverter defibrillator, creatinine level of 1.2 mg/dL or less, and left ventricular end-diastolic dimension less than 6.5 cm. Topkara et al (2016) reported a similar analysis of 13,454 INTERMACS adults with implants between June 2006 and June 2015 without TAH or pulsatile-flow LVAD or heart transplant. Device explant rates for cardiac recovery were 0.9% at 1-year, 1.9% at 2-year, and 3.1% at 3-year follow-up. Predictors of recovery were similar to Wever-Pinzon (2016). An additional 9% of patient demonstrated partial cardiac recovery.

A number of relatively small, noncomparative studies have evaluated LVADs as bridge-to-recovery therapy. In 2006 case series, Birks et al evaluated 15 patients with severe heart failure due to nonischemic cardiomyopathy underwent implantation of LVADs, along with medical management designed to enhance myocardial recovery. Eleven of 15 patients had enough myocardial recovery to undergo LVAD explantation; two died after explantation. Among those who survived, the cumulative rate of freedom from recurring heart failure was 100% and 88.9%, respectively, at 1 and 4 years postexplantation. In 2011, the same group subsequently reported results of their LVAD explantation protocol among patients with severe heart failure due to nonischemic cardiopathy who had nonpulsatile LVADs implanted. They included 20 patients who received a combination of angiotensin-converting enzyme inhibitors, β-blockers, and adosterol antagonists followed by the β2-agonist clenbuterol. One patient, lost to follow-up, died after 240 days of
support. Of the remaining 19 patients, 12 (63.2%) were successfully explanted after a mean 286 days; estimated survival without heart failure recurrence was 83.3% at both 1 and 3 years. In a prospective multicenter study to assess myocardial recovery in patients with LVAD implantation as a bridge to transplant, Maybaum et al (2007) evaluated 67 patients with heart failure who had undergone LVAD implantation for severe heart failure. After 30 days, patients demonstrated significant improvements compared with their pre-LVAD state in left ventricular ejection fraction (17.1% vs 34.12%, p<0.001), left ventricular end-diastolic diameter (7.1 cm vs 5.1 cm, p<0.001), and left ventricular mass (320 g vs 194 g, p<0.001), respectively. However, only 9% of patients demonstrated sufficient recovery to have their LVAD explanted.

Takayama et al (2014) reported outcomes for a retrospectively defined cohort of 143 patients who received a CentriMag Right Ventricular Assist Device as a “bridge to decision” for refractory cardiogenic shock due to a variety of causes. Patients were managed with a bridge to decision algorithm. Causes of cardiogenic shock included failure of medical management (n=71), postcardiotomy shock (n=37), graft failure after heart transplantation (n=2), and right ventricular failure postimplantable LVAD (n=13). The device configuration was biventricular in 67%, isolated right VAD in 26%, and isolated LVAD in 8%. After a mean duration of support of 14 days (interquartile range, 8-26 days), 30% of patients had myocardial recovery, 15% had device exchange to an implantable VAD, and 18% had a heart transplant.

In a smaller single-center retrospective cohort study, Mohamedali et al (2015) reported outcomes for 48 patients treated with biventricular support with the CentriMag device as a “bridge to decision”, 18 of whom had biventricular support with venoarterial extracorporeal membrane oxygenation (ECMO), while the remainder received only biventricular VAD support. Overall, 23 patients were explanted, 9 to recovery, 14 to a durable LVAD, with 3 additional patients explanted for withdrawal of care.

**Section Summary: VADs as Bridge to Recovery**

There has been interest in prospectively identifying subsets of patients who might benefit from a temporary VAD with the goal of bridging to recovery. Available studies have indicated that a subset of patients who receive a VAD as a bridge to transplant or as destination therapy have demonstrated improvements in their cardiac function, sometimes to the point that they no longer require the VAD. However, questions remain about defining and identifying the population most likely to experience cardiac recovery with VAD placement. One clearly-defined population in which the potential for myocardial recovery exists is in the postcardiotomy setting. The current evidence is insufficient to identify other heart failure patient populations that might benefit from the use of an LVAD as a specific bridge to recovery treatment strategy.

**VADs as Bridge to Transplant**

The insertion of a VAD will categorize its recipient as a high-priority heart transplant candidate. The available evidence on the efficacy of VADs in bridging patients with refractory heart failure to transplant includes single-arm series, which generally have reported high success rates in bridging to transplant.
Adult Patients

A 1996 TEC Assessment concluded that VADs can provide an effective bridge to transplantation. Goldstein et al (1998) published a slightly more recent review.

In 2011, Strueber et al. published a case series of 50 patients awaiting heart transplantation treated with HeartWare Ventricular Assist System, which is a smaller, continuous-flow centrifugal device implanted in the pericardial space. Patients were followed until transplantation, myocardial recovery, device explant, or death. The median duration of time on the VAD was 322 days. Nine patients died: three from sepsis, three from multiple organ failure, and three from hemorrhagic stroke. At the end of follow-up, 20 (40%) patients had undergone transplant, 4 (8%) had the pump explanted, and the remaining 17 (34%) continued on pump support. The most common complications were infection and bleeding: 21 (42%) patients had infections, 5 (10%) had sepsis, while 15 patients (30%) had bleeding from complications, 10 (20%) of whom required surgery.

In 2012, Aaronson et al reported results of a multicenter, prospective study of a newer generation LVAD, the HeartWare. The study enrolled 140 patients awaiting heart transplantation who underwent HeartWare implantation. A control group of 499 subjects comprised patients drawn from the INTERMACS database, which collects data on patients who receive FDA-approved durable MCS devices. The study’s primary outcome was defined as survival on the originally implanted device, transplantation, or explantation for ventricular recovery at 180 days. Secondary outcomes were comparisons of survival between groups and functional, quality of life (QOL), and adverse event outcomes in the HeartWare group. Success on the primary outcome occurred in 90.7% of the HeartWare group and 90.1% of controls (p<0.001, noninferiority with a 15% margin). Serious adverse events in the HeartWare group included, most commonly, bleeding, infections, and perioperative right heart failure.

In 2013, Slaughter et al reported combined outcomes for patients included in the HeartWare bridge to transplant study previously described and a continued-access protocol granted by FDA. The study included 322 patients with heart failure, eligible for heart transplant, who received the HeartWare (140 patients from the original study; 190 patients in the continue-access protocol who were monitored to outcome or had completed 180-day follow-up at the time of analysis). Survival at 60, 180, and 360 days was 97%, 91%, and 84%, respectively. The most common adverse events were respiratory dysfunction, arrhythmias, sepsis, and driveline exit-site infections. Patients generally had improvements in QOL measures.

In 5 reports published from 2007 to 2008, with sample sizes ranging from 32 to 279 patients, most participants received the continuous-flow device as a bridge to transplantation. Survival rates at 6 months ranged between 67% and 87%, and between 50% and 80% at 1 year. These rates were similar to those reported from the INTERMACS registry. An additional 2011 report from INTERMACS comparing the HeartMate II with other LVADs for patients who received them as a bridge to transplantation reported that 91% and 80% of HeartMate II and other LVAD patients,
respectively, reached transplant, cardiac recovery, or ongoing LVAD support by 6 months. A study by Patel et al (2008) compared HeartMate I and HeartMate II recipients at a single center, finding similar rates of 1-year survival and subsequent development of right heart failure. Serious adverse events occurring after HeartMate II implantation include bleeding episodes requiring reoperation, stroke, infection, and device failure.

**Effects of Pretransplant VADs on Transplant Outcomes**

Published studies continue to report that the use of a VAD does not compromise the success of a subsequent heart transplant and, in fact, may improve post-transplant survival, thus improving the use of donor hearts. A systematic review published in 2011 examined the evidence on the effect of VADs on posttransplant outcomes. Reviewers included 31 observational studies that compared transplant outcomes in patients who did and did not have pretransplant VAD. Survival at 1 year was more likely in patients who had VAD treatment, but this benefit was specific to patients who received an intracorporeal device (relative risk [RR], 1.8; 95% confidence interval [CI], 1.53 to 2.13). For patients treated with an extracorporeal device, the likelihood of survival did not differ from patients not treated with a VAD (RR=1.08; 95% CI, 0.95 to 1.22). There was no difference in the risk of rejection rates between patients who did and did not receive LVAD treatment.

In 2014, Deo et al reported no significant differences in outcomes for 37 bridge to transplant patients with a VAD and 70 patients who underwent a heart transplant directly. Data from the United Network for Organ Sharing, reported by Grimm et al (2016), suggested that patients bridged to transplant with an LVAD have better outcomes than those bridged with TAHs or biventricular assist devices.

**Pediatric patients**

The FDA-approved EXCOR Pediatric VAD is available for use as a bridge to cardiac transplant in children. FDA approval was based on data from children who were a part of the initial clinical studies of this device. Publications have reported positive outcomes for children using VADs as a bridge to transplantation.

**Comparative Studies**

Following FDA approval, Fraser et al (2012) evaluated the EXCOR device among 48 children, aged 16 or younger with 2-ventricle circulation who had severe heart failure, despite optimized treatment, and were listed for heart transplant. Patients were divided into 2 groups based on body surface area (BSA); a historic control group of children, receiving circulatory support with ECMO from the Extracorporeal Life Support Organization registry, were matched in a 2:1 fashion with study participants based on propensity-score matching. For participants in cohort 1 (BSA<0.7 m²), the median survival time had not been reached at 174 days, while in the matched ECMO comparison group, the median survival was 13 days (p<0.001). For participants in cohort 2 (BSA range 0.7 to <1.5 m²), the median survival was 144 days, compared with 10 days in the matched ECMO group (p<0.001). Rates of adverse events were high in both EXCOR device cohorts, including major bleeding (42% and 50% of cohort 1 and cohort 2, respectively), infection (63% and 50% of cohort 1 and cohort 2), and stroke (29% of both cohorts), all respectively.
In 2016, Wehman et al reported on posttransplant survival outcomes for pediatric patients who received a VAD, ECMO, or no MCS, in the pretransplant period. The study included 2777 pediatric patients who underwent heart transplant from 2005 to 2012 who were identified through the United Network for Organ Sharing database, of whom 428 were bridged with VADs and 189 were bridged with ECMO. In unadjusted analysis, the actuarial 5-year survival was highest in the direct-to-transplant group (77%), followed by the VAD group (49%) and then the ECMO group (35%). In a proportional hazards model to predict time to death, restricted to the first 4 months posttransplant, ECMO bridging was significantly associated with higher risk of death (adjusted hazard ratio, 2.77 vs direct-to-transplant; 95% CI, 2.12 to 3.61; p<0.001). However, a model to predict time to death excluding deaths in the first 4 months posttransplant, the bridging group was not significantly associated with risk of death.

Bulic et al (2017) identified all U.S. children between 1 and 21 years of age at heart transplant between 2006 and 2015 for dilated cardiomyopathy who were supported with an LVAD or vasoactive infusions alone at the time of transplant from the Organ Procurement and Transplant Network registry (n=701). Children receiving LVAD were older, on a higher level of hemodynamic support, more likely to be on dialysis, and waited longer to receive a donor heart than children receiving vasoactive infusions. Functional status as measured by the median Karnofsky Performance Scale score at heart transplant was higher for children receiving LVAD (6) compared with vasoactive infusion (5; p<0.001) and children receiving LVAD were more likely to be discharged from the hospital at the time of transplant. The percentage of children having stroke at the time of transplant was higher in those receiving LVAD (3% vs 1%, p=0.04).

**Noncomparative Studies**

In 2016, Blume et al published the first analysis of the Pediatric Interagency Registry for Mechanical Circulatory Support, which is a prospective, multicenter registry that collects data on patients who are under age 19 at the time of implant, and includes those implanted with either durable or temporary VADs. At the time of analysis, the registry included 241 patients; of these, 41 were implanted with a temporary device only, leaving 200 patients implanted with VADs for the present study. Most patients (73%) had an underlying diagnosis of cardiomyopathy. At the time of implantation, 64% were listed for transplant, while 29% were implanted with a “bridge to candidacy” strategy. A total of 7% were implanted with a destination therapy strategy. Actuarial survival at both 6 months and 1 year was 81%. By 6 months, 58% of patients had received transplants.

In 2013, Almond et al reported results from a prospective, multicenter registry to evaluate outcomes in children who received the EXCOR device as a bridge to transplant. This study included a broader patient population than the Fraser study (discussed above). All patients were followed from the time of EXCOR implantation until transplantation, death, or recovery. The study included 204 children, 67% of whom received the device under compassionate use. Survival at 12 months on EXCOR support was 75%, including 64% who survived to transplantation, 6% who recovered (device explanted and patient survived 30 days), and 5% who were alive with the device in place. In a 2015
follow-up study that evaluated 204 children from the same registry, Jordan et al reported relatively high rates of neurologic events in pediatric patients treated with the EXCOR device (29% of patients), typically early in the course of device use.

In 2016, Chen et al reported on a retrospective, single-center series of pediatric patients with continuous-flow VADs, with a focus on outpatient experiences. The series included 17 children implanted with an intracorporeal device from 2010 to 2014. Eight (47%) patients were discharged after a median postimplant hospitalization duration of 49 days. Adverse events were common in outpatients, most frequently major device malfunction (31% [5/16] events) and cardiac arrhythmias (31% [5/16] events). At the time of analysis, 4 patients had received an orthotopic heart transplant, two were on ongoing support, and one each had been transferred or died.

Another 2016 retrospective, single-center series of pediatric patients reported on outcomes with short-term continuous-flow VADs, including the Thoratec PediMag or CentriMag, or the Maquet RotaFlow. From 2015 to 2014, 27 children were supported with one of these devices, most commonly for congenital heart disease (42%). The median duration of support was 12 days, and 67% of all short-term continuous-flow VAD runs (19 of 28 runs) led to hospital discharge.

Using the United Network for Organ Sharing database, Davies et al (2008) reported on the use of VADs in pediatric patients undergoing heart transplantation. Their analysis concluded that pediatric patients requiring a pretransplantation VAD have similar long-term survival similar to those not receiving MCS.

Section Summary: VADs as Bridge to Transplant
In adults, the evidence on the efficacy of LVADs as bridge to transplant consists of uncontrolled trials, registry studies, and case series. In children, the evidence consists of several uncontrolled trials and a trial with historical controls. Collectively, these studies have reported that substantial numbers of patients have survived to transplant in situations in which survival is historically low. Despite the lack of high-quality controlled trials, this evidence supports a finding that outcomes are improved in patients because they have no other treatment options.

VADs as Destination Therapy

Randomized Controlled Trials
The evaluation of VADs as destination therapy was informed by a 2002 TEC Assessment that offered the following observations and conclusions:

- The available evidence comes from a single, well-designed and rigorously conducted randomized trial, known as the REMATCH study. The trial was a cooperative effort of Thoratec, Columbia University, and the National Institutes of Health.
- The trial found that patients with end-stage heart failure who are not candidates for cardiac transplantation had significantly better survival on a VAD compared with treatment by optimal medical therapy. Median survival was improved by approximately 8.5 months. Serious
adverse events were more common in the VAD group, but these appear to be outweighed by this group’s better outcomes on function; New York Heart Association class was significantly improved, as was QOL among those living to 12 months.

- VAD patients spend a greater relative proportion of time inside the hospital than medical management patients do, but the survival advantage would mean a longer absolute time outside the hospital.

Park and colleagues (2005) published reports on extended 2-year follow-up of patients from the REMATCH trial, which found that survival and QOL benefits were still apparent. In addition, their reports and other case series have suggested continuing improvement in outcomes related to ongoing improvements in the device and in patient management. However, the durability of the Heartmate device used in the REMATCH trial was a concern (eg, at one participating institution, all 6 long-term survivors required device change-outs).

**Nonrandomized Comparative Studies**

After release of the REMATCH trial results, Rogers et al (2007) published results from a prospective, nonrandomized trial comparing LVAD as destination therapy with optimal medical therapy for patients with heart failure who were not candidates for heart transplant. Fifty-five patients who had New York Heart Association functional Class IV symptoms and who failed weaning from inotropic support were offered a Novacor LVAD; 18 did not receive a device due to preference or device unavailability and acted as a control group. The LVAD-treated patients had superior survival rates at 6 months (46% vs 22%; p=0.03) and 12 months (27% vs 11%; p=0.02), along with fewer adverse events.

A subsequent prospective observational study called the Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients study comparing LVAD support (n=97) to optimal medical therapy (n=103) for patients with heart failure not requiring inotropes also reported superior survival and health-related QOL in LVAD-treated patients. Twelve-month, as-treated, event-free actuarial survival was 80% in the LVAD group compared with 63% in the best medical therapy group (p=0.022). Two-year results from this study were reported in 2017. At the end of 2 years, 35 (34%) medical therapy patients and 60 (62%) LVAD patients were alive on their original therapy; 23 medical management patients received LVADs during the 2 years. The LVAD-treated patients continued to have higher as-treated, event-free actuarial survival (70% vs 41%, p<0.001) although there was no difference in intention-to-treat survival (70% vs 63%, p=0.31).

**Noncomparative Studies**

In an FDA-required postapproval study of the HeartMate II device for destination therapy, which included the first 247 HeartMate II patients identified as eligible for the device as destination therapy, outcomes and adverse events did not differ significantly from those of the original trial, which compared patients who received the HeartMate II with earlier generation devices (Slaughter et al [2009], described below). Survival rates in the postapproval cohort were 82% and 69% at 1 and 2 years postoperatively, respectively.
Arnold et al (2016) analyzed 1638 patients receiving LVADs as destination therapy between May 2012 and September 2013. Results were selected from the INTERMACS registry and assessed for poor outcomes. Poor outcome was defined as death or mean Kansas City Cardiomyopathy Questionnaire overall score less than 45 throughout the year after implantation. Analyses included inverse probability weighting to adjust for missing data. About 22.4% of patients died within the first year after implantation, and an additional 7.3% had persistently poor QOL; 29.7% met the definition of poor outcome. Poor outcomes were more common in those patients having higher body mass indices, lower hemoglobin levels, previous cardiac surgery, history of cancer, severe diabetes, and poorer QOL preimplant.

Section Summary: VADs as Destination Therapy
The highest quality evidence on the efficacy of LVADs as destination therapy in patients who are not transplant candidates is the REMATCH trial. This multicenter RCT reported that the use of LVADs led to improvements in survival, QOL, and functional status. This evidence supports a finding that health outcomes are improved with LVADs in this patient population.

Comparative Efficacy: Bridge to Transplant or Destination Therapy
The mechanism of operation of LVADs has changed since their introduction. The earliest devices were pulsatile positive displacement pumps. The pulsatile pumps have been largely replaced by axial continuous-flow pumps. More recently centrifugal continuous-flow pumps have also been introduced.

Centrifugal Continuous-Flow vs Axial Continuous-Flow
Two RCTs (MOMENTUM3, ENDURANCE) published in 2017 have compared centrifugal continuous-flow circulatory pumps with an axial continuous-flow pump (HeartMate II). Trial characteristics and results are shown in Tables 2 and 3, respectively. Funding was provided by St. Jude Medical for MOMENTUM3 and by HeartWare for ENDURANCE. Both trials used a similar composite primary outcome but differed by lengths of follow-up. In MOMENTUM3, the composite was defined as survival free of disabling stroke or survival free of reoperation to replace or remove the device at 6 months after implantation. In ENDURANCE, the composite was defined as survival free from disabling stroke with the originally implanted device at 2 years. Both trials found the centrifugal device to be noninferior to the axial device with respect to the primary, composite outcome and found the centrifugal device had fewer malfunctions and required fewer reoperations. The ENDURANCE trial found an increased risk of death by 2 years (35% vs 26%) that was not statistically significant and significant increases in patients experiencing stroke, sepsis, and right heart failure with the centrifugal vs axial device. Both trials reported similar improvements in functional and QOL outcomes in both groups.

<table>
<thead>
<tr>
<th>Author</th>
<th>Study (Registration)</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Centrifugal-Flow Pump</th>
<th>Key Eligibility Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mehra et al (2017)</td>
<td>MOMENTUM3 (NCT02224755)</td>
<td>U.S.</td>
<td>69</td>
<td>2014-2015</td>
<td>HeartMate 3</td>
<td>Advanced heart failure refractory to standard medical therapy; included patients receiving pump as bridge to transplant or as destination therapy</td>
</tr>
<tr>
<td>Rogers et al (2017)</td>
<td>ENDURANCE (NCT01166347)</td>
<td>U.S.</td>
<td>48</td>
<td>2010-2012</td>
<td>HeartWare</td>
<td>Advanced heart failure refractory to standard medical therapy; LVEF</td>
</tr>
</tbody>
</table>
LVEF: left ventricular ejection fraction; MOMENTUM3: Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3; ENDURANCE; RCT: randomized controlled trial.

Table 3. RCT Trial Results for Centrifugal vs Axial Continuous-Flow Devices

<table>
<thead>
<tr>
<th>Study</th>
<th>Number Randomized</th>
<th>Composite Outcome: Survival With No Stroke or Reoperation</th>
<th>p</th>
<th>Functional Status/QOL</th>
<th>Adverse Events</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Composite at 6 mo:</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>86% vs 77%</td>
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<tr>
<td></td>
<td></td>
<td>o 0.55 (0.32 to 0.95)</td>
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<tr>
<td></td>
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<td>o 1.31 (0.37 to 4.64)</td>
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<td></td>
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<td>Reoperation: 1% vs 8%</td>
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<td></td>
<td></td>
<td>o 0.08 (0.01 to 0.60)</td>
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<td>o 0.82 (0.38 to 1.73)</td>
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<td></td>
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<td>Composite at 2 years:</td>
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<tr>
<td></td>
<td></td>
<td>55% vs 57%</td>
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<td></td>
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<td>o Difference, 3.7% (12.6%)</td>
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<tr>
<td></td>
<td></td>
<td>Disabling stroke: 3% vs 0%</td>
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<tr>
<td></td>
<td></td>
<td>Device malfunction or failure: 9% vs 16%</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>Death: 35% vs 26%</td>
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</tbody>
</table>

EQ-5D: European Quality of Life–5 Dimensions; KCCQ: Kansas City Cardiomyopathy Questionnaire; LVAD: left ventricular assist device; NYHA: New York Heart Association; QOL: quality of life; RCT: randomized controlled trial; VAS: visual analog scale; LVAS: left ventricular assist system.

Continuous-Flow Vs Pulsatile-Flow Devices

In 2009, Slaughter et al published data from an unblinded randomized multicenter trial. Subjects were randomized to continuous-flow or pulsatile-flow devices on a 2:1 block-randomization basis. The primary outcome measured was a composite end point of 2-year survival, freedom from disabling stroke, or need for device replacement. The primary outcome was reached by continuous-flow patients (n=134) at a rate of 46% (95% CI, 38% to 55%) while pulsatile-flow patients (n=66) reached that outcome at a rate of 11% (95% CI, 3% to 18%); the difference was statistically significant (p<0.001). Analysis of constituent factors indicated that a lower rate of devices needing replacement in the continuous-flow group had the largest effect on the composite end point; 2-year death rate also favored this device (58% vs 24%, respectively; p=0.008). Stroke and death rates (within 2 years of implantation) were similar in the 2 groups (stroke rate, 12%; death rate, 36%). QOL scores were also similar.

Nativi et al (2011) published a nonrandomized comparison of pulsatile- vs continuous-flow devices using data on 8557 patients undergoing transplant from the registry of the International Society for Heart and Lung Transplantation. Comparisons were made among patients receiving a pulsatile LVAD, a continuous-flow LVAD, and no LVAD. Two time periods were analyzed: pre-2004, when nearly all LVADs were pulsatile devices, and post-2004, when continuous use devices were introduced into clinical care. Comparing the time periods, there was a significantly greater risk of
mortality in the first than in the second (RR=1.30; 95% CI, 1.03 to 1.65; p=0.03). When the analysis was confined to the second time period, there was no significant improvement in survival for the continuous group compared with the pulsatile group (RR=1.25; 95% CI, 1.03 to 1.65; p=0.03).

Dell’Aquila et al (2014) compared outcomes for patients treated with a third-generation continuous-flow device (HeartWare) to those for patients treated with older devices (older continuous-flow or pulsatile-flow devices) in a single-center study. Of 287 patients who received VAD support from 1993 to 2012, 52 received a HeartWare device, 76 an older continuous-flow device, and 159 an older pulsatile device. Survival was significantly better for patients who received a third-generation device, with 24-month survival rate of 70.4%, compared with 33.7% for patients who received an older continuous-flow device and 33.8% for those who received an older pulsatile-flow device (p=0.013). The difference in survival associated with third-generation devices was more pronounced for higher scores on the INTERMACs scale.

Other nonrandomized studies that have compared outcomes from different types of LVADs have been smaller and/or focused on physiologic outcomes. In some of these studies, the continuous-flow devices exhibited greater improvement in physiologic measures, but none reported significant differences in clinical outcomes between devices.

Section Summary: Comparative Efficacy
The evidence of the comparative efficacy of centrifugal continuous-flow vs axial continuous-flow devices consists of 2 RCTs of 2 different centrifugal continuous-flow devices. The MOMENTUM3 trial compared HeartMate 3 centrifugal continuous-flow device with the HeartMate II axial continuous-flow device in patients indicated for circulatory support as a bridge to transplant or destination therapy. HeartMate 3 is not currently FDA-approved. The ENDURANCE trial compared HeartWare centrifugal continuous-flow device with the HeartMate II axial continuous-flow device in patients indicated for circulatory support as destination therapy. HeartWare is FDA-approved for bridge to transplantation. Both trials found the centrifugal device to be noninferior to the axial device for the primary, composite outcome including measures of survival, freedom from disabling stroke, and freedom from device failure. While there are fewer device failures with the centrifugal devices without significant increase in disabling stroke, the HeartWare device was associated with increased risk of any stroke over a period of 2 years.

The evidence on the comparative efficacy of continuous-flow vs pulsatile-flow devices consists of an RCT and several nonrandomized comparative studies. The RCT reported fairly large differences in a composite outcome measure favoring the continuous-flow devices, with increases in revision and reoperation rates for the pulsatile device group being the largest factor driving the difference in outcomes. Other nonrandomized comparative studies, including a database study with large numbers of patients, have not reported important differences in clinical outcomes between devices.

TOTAL ARTIFICIAL HEARTS

TAH as Bridge to Transplant
FDA approval of the CardioWest TAH was based on the results of a nonrandomized, prospective study of 81 patients. Patients had failed inotropic therapy, had biventricular failure, and thus were not considered appropriate candidates for an LVAD. The rate of survival to transplant was 79%, which was considered comparable to the experience with LVAD in patients with left ventricular failure. The mean time from entry into the study until transplantation or death was 79.1 days.

Other case series have been reported on outcomes for the TAH as a bridge to transplant. For example, Copeland et al (2012) reported on 101 patients treated with the SynCardia artificial heart as a bridge to transplant. All patients either met established criteria for MCS, or were failing medical therapy on multiple inotropic drugs. Mean support time was 87 days (range, 1-441 days). The rate of survival to transplant was 68.3% (69/101). Of the 32 deaths before transplant, 13 were due to multiple organ failure, 6 were due to pulmonary failure, and 4 were due to neurologic injury. Rates of survival after transplant at 1, 5, and 10 years, respectively, were 76.8%, 60.5%, and 41.2%.

**TAH as Destination Therapy**

Data on the artificial heart are available from FDA approval information and from a published article describing results for the first 7 patients. FDA indicated that its decision on the AbioCor implantable heart was based on the manufacturer’s (Abiomed) laboratory and animal testing and on a small clinical study of 14 patients conducted by Abiomed. Study participants had a 1-month survival prognosis of not more than 30%, were ineligible for cardiac transplants, and were not projected to benefit from VAD therapy. The study showed that the device was safe and likely to benefit for people with severe heart failure whose death is imminent and for whom no alternative treatments are available. Of the 14 patients studied, 12 survived surgery. Mean duration of support for the patients was 5.3 months. In some cases, the device extended survival by several months (survival was 17 months in 1 patient). Six patients were ambulatory; 1 patient was discharged home. Complications included postoperative bleeding and neurologic events. No device-related infection was reported.

Torregrossa et al (2014) reported on 47 patients who received a TAH at 10 worldwide centers and had the device implanted for more than 1 year. Patients were implanted for dilated cardiomyopathy (n=23), ischemic cardiomyopathy (n=15), and “other” reasons (n=9). Over a median support time of 554 days (range, 365-1373 days), 34 (72%) patients were successfully transplanted, 12 (24%) patients died while on device support, and 1 (2%) patient was still supported. Device failure occurred in 5 (10%) patients. Major complications were common, including systemic infection in 25 (53%) patients, driveline infections in 13 (27%) patients, thromboembolic events in 9 (19%) patients, and hemorrhagic events in 7 (14%) patients. Two of the deaths occurred secondary to device failure.

**Section Summary: Total Artificial Hearts**

There is less evidence on the use of TAH as a bridge to transplant and as destination therapy compared with the use of LVADs. The type of evidence on bridge to transplant is similar to that for LVADs (ie, case series reporting substantial survival rates in patients without other alternatives). Therefore, similar to LVADs, this evidence is sufficient to conclude that TAH improves outcomes for
these patients and TAH is a reasonable alternative for patients who require bridge to transplantation but who are ineligible for other types of support devices.

Although TAHs show promise as destination therapy in patients who have no other treatment options, the available data on their use is extremely limited. Currently, the evidence base on the use of TAH as destination therapy is insufficient to support conclusions about TAH efficacy in this setting.

PERCUTANEOUS VENTRICULAR ASSIST DEVICES

pVADS as an Alternative to Intra-Aortic Balloon Pump for cardiogenic shock.

Systematic Reviews
Romeo et al (2016) reported on a systematic review and meta-analysis that evaluated various percutaneous mechanical support methods, including pVADs, for patients with cardiogenic shock due to AMI who were undergoing revascularization. Reviewers included the 3 RCTs (described below) comparing pVADs with intra-aortic balloon pumps (IABPs), along with 3 observational studies. In the comparison of pVADs with IABP, the reviewers found that in-hospital mortality (the primary outcome of the analysis) was nonsignificantly increased in the pVAD group.

A 2009 meta-analysis by Chen et al included the same 3 trials as Romeo (2016). None of the 3 trials reported an improvement in mortality associated with pVAD use. The combined analysis estimated the RR for death in pVAD patients as 1.06 (95% CI: 0.68-1.66, p=0.80). All 3 trials reported an improvement in left ventricle hemodynamics in the pVAD group. On combined analysis, there was a mean increase in cardiac index of 0.35 L/min/m^2 for the pVAD group, an increase in mean arterial pressure of 12.8 mm Hg (95% CI: 3.6-22.0 mm Hg; p<0.001), and a decrease in pulmonary capillary wedge pressure of 5.3 mm Hg (95% CI: 1.2-9.4 mm Hg; p<0.05). Complications were more common in the pVAD group. On combined analysis, patients in the pVAD group had a significantly increased likelihood of bleeding events (RR=2.35; 95% CI: 1.40-3.93). Leg ischemia was also more common in the pVAD group, but this difference was not statistically significant (RR= 2.59, 95% CI: 0.75-8.97, p=0.13).

Randomized Controlled Trials
Four RCTs have compared pVADs with IABPs for patients with cardiogenic shock; three were included in the systematic reviews described above, and one was published after the reviews. The 4 RCTs enrolled a total of 148 patients, 77 treated with a pVAD and 71 treated with an IABP. All 4 trial populations included patients with AMI and cardiovascular shock; 1 trial restricted this population to patients who were postrevascularization in the AMI setting. The primary outcomes reported were 30-day mortality, hemodynamic measures of left ventricle pump function, and adverse events. The trials are summarized in Tables 4 and 5. Some trials reported improvements in hemodynamic and metabolic parameters, but none found any improvement in 30-day mortality. The IMPRESS trial reported 6-month mortality outcomes and also found no difference between groups. Bleeding events and leg ischemia were more common in the pVAD groups.
Table 4. Characteristics of RCTs Comparing pVADs With IABPs for Patients With Cardiogenic Shock

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Study (Registration)</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>pVAD</th>
<th>Key Eligibility Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burkhoff et al (2006)</td>
<td>TandemHeart (NR)</td>
<td>U.S.</td>
<td>12</td>
<td>2002-2004</td>
<td>TandemHeart</td>
<td>CS &lt;24 h due to MI or heart failure</td>
</tr>
<tr>
<td>Thiele et al (2005)</td>
<td>NR</td>
<td>Germany</td>
<td>1</td>
<td>2000-2003</td>
<td>TandemHeart</td>
<td>AMI with CS and intent to revascularize with PCI</td>
</tr>
<tr>
<td>Ouweneel et al (2017)</td>
<td>IMPRESS (NTR3450)</td>
<td>Netherlands, Norway</td>
<td>2</td>
<td>2012-2015</td>
<td>Impella CP</td>
<td>AMI and severe CS in the setting of immediate PCI; receiving mechanical ventilation</td>
</tr>
</tbody>
</table>

AMI: acute myocardial infarction; CS: cardiogenic shock; IABP: intra-aortic balloon counterpulsation; IMPRESS: IMPella versus IABP Reduces mortality in STEMI patients treated with primary PCI in Severe cardiogenic SHOCK; ISAR-SHOCK: Efficacy Study of LV Assist Device to Treat Patients With Cardiogenic Shock; MI: myocardial infarction; NR: not reported; PCI: percutaneous coronary intervention; pVAD: percutaneous ventricular assist device; RCT: randomized controlled trial.

Table 5. RCT Results Comparing pVADs With IABPs for Patients With Cardiogenic Shock

<table>
<thead>
<tr>
<th>Study</th>
<th>Numbers Randomized</th>
<th>Mortality (pVAD vs IABP)</th>
<th>Bleeding</th>
<th>Leg Ischemia</th>
<th>Other Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>TandemHeart</td>
<td>pVAD: 19 IABP: 14</td>
<td>30-day:</td>
<td>42% vs 14%</td>
<td>21% vs 14%</td>
<td>At least 1 adverse event: 95% vs 71%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 47% vs 36%</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>ISAR-SHOCK</td>
<td>pVAD: 13 IABP: 13</td>
<td>30 day:</td>
<td>NR</td>
<td>8% vs 0%</td>
<td>Increase in cardiac index (L/min/m²): 0.49±0.46 vs 0.11±0.031</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 46% vs 46%</td>
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<td></td>
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</tr>
<tr>
<td>Thiele et al (2005)</td>
<td>pVAD: 21 IABP: 20</td>
<td>30-day:</td>
<td>90% vs 40%</td>
<td>33% vs 0%</td>
<td>Final cardiac index (W/m²): 0.37 vs 0.28</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 43% vs 45%</td>
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<tr>
<td>IMPRESS</td>
<td>pVAD: 24 IABP: 24</td>
<td>30-day:</td>
<td>33% vs 8%</td>
<td>NR</td>
<td>Rehospitalization: 21% vs 4%</td>
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<tr>
<td></td>
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<td>• 46% vs 50%</td>
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<td>• HR=0.96 (0.42 to 2.18)</td>
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<td>60-day:</td>
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<tr>
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<td>• 50% vs 50%</td>
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<td>• HR=1.04 (0.47 to 2.32)</td>
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</tbody>
</table>

AMI: acute myocardial infarction; IABP: intra-aortic balloon counterpulsation; IMPRESS: IMPella versus IABP Reduces mortality in STEMI patients treated with primary PCI in Severe cardiogenic SHOCK; IQR: interquartile range; ISAR-SHOCK: Efficacy Study of LV Assist Device to Treat Patients With Cardiogenic Shock; NR: not reported; pVAD: percutaneous ventricular assist devices; RCT: randomized controlled trial; HR: hazard ratio.

Registry Studies and Case Series

O’Neill et al (2014) compared outcomes for patients who had AMI complicated by cardiogenic shock who received pVAD support before percutaneous coronary intervention (PCI) with those who received pVAD support after PCI using data from 154 consecutive patients enrolled in a multicenter registry. Patients who received pVAD support pre-PCI had a higher survival to discharge rate (65.1%) than those who received pVAD support post-PCI (40.7%; p=0.003. In multivariable analysis, receiving pVAD support pre-PCI was associated with in-hospital survival (odds ratio [OR], 0.37; 95% CI, 0.17 to 0.79; p=0.01). However, the potential for underlying differences in patient groups other than the use of pVAD support makes the study’s implications uncertain.

Basir et al (2017) compared survival in patients with AMI complicated by cardiogenic shock and undergoing PCI who received an Impella device. Exactly 287 consecutive patients from the global cVAD Registry were analyzed. Impella implantation before and after PCI and before initiation of inotropes or vasopressors was independently associated with survival in multivariate analysis. Survival rates were 66% in patients who received the Impella device less than 1.25 hours from shock onset, 37% in those receiving the device within 1.25 to 4.25 hours, and 26% after 4.25 hours (p=0.017).
Case series of patients treated with pVADs as an alternative to IABP in cardiogenic shock have reported high success rates as a bridge to alternative therapies. However, given the availability of RCT evidence, these studies add a limited amount to the body of evidence on the efficacy of pVADs for the management of cardiogenic shock.

**Section Summary: pVADs as an Alternative to Intra-Aortic Balloon Pump for Cardiogenic Shock**

Four RCTs comparing pVAD with IABP for patients in cardiogenic shock and meta-analyses including three of these RCTs failed to demonstrate a mortality benefit for pVAD use and reported higher complications associated with pVAD use.

**pVADs as Ancillary Support in High-risk Patients Undergoing High-Risk Cardiovascular Procedures**

**Systematic Reviews**

In 2016, Briasoulis et al reported on a meta-analysis of pVAD devices as an adjunct to high-risk PCI. The reviewers included RCTs and cohort studies, identifying 18 nonrandomized observational studies and a single RCT. The RCT identified was the PROTECT II trial detailed below. In the observational studies, the sample sizes ranged from 7 to 637 patients. In pooled analysis, the 30-day mortality rate following Impella-assisted high-risk PCI was 3.5% (95% CI, 2.2% to 4.8%; $I^2=20\%$), while that for TandemHeart-assisted high-risk PCI was 8% (95% CI, 2.9% to 13.1%; $I^2=55\%$). The pooled vascular complication rates were 4.9% (95% CI, 2.3% to 7.6%) and 6.5% (95% CI, 3.2% to 9.9%) for the Impella and the TandemHeart, respectively.

**Randomized Controlled Trials**

The PROTECT II trial, planned as an RCT, compared the Impella system with IABP in patients undergoing high-risk PCI procedures. Enrollment was planned for 654 patients from 50 clinical centers. The primary endpoint was the composite of 10 different complications occurring within 30 days of the procedure, with the trialists hypothesizing a 10% absolute decrease in the complication rate for patients in the pVAD group. The trial was discontinued prematurely in late 2010 due to futility after an interim analysis of the first 327 patients enrolled revealed that the primary end point could not be reached. When stopped, 452 patients had been enrolled, three of whom withdrew consent and one of whom died. Results were published by O’Neill et al in 2012. The trial’s primary analysis was intention to treat and included all 448 patients randomized to the Impella system (n=225) or IABP (n=223). The primary composite end point of major adverse events at 30 days occurred in 35.1% of Impella patients and in 40.1% of the IABP patients (p=0.277). There was no significant difference in the occurrence of in-hospital death, stroke, or myocardial infarction between the Impella patients and the IABP patients.

In a prespecified subgroup analysis of the PROTECT II trial, Kovacic et al (2015) compared outcomes for the Impella system and IABP among 325 patients with 3-vessel disease with a left ventricular ejection fraction of 30% or less. In the 3-vessel disease subgroup, 167 subjects were randomized to PCI with Impella support and 158 to PCI with IABP support. PCI characteristics differed in that rotational atherectomy was more aggressively used in the Impella-support group, with more passes...
per patient (5.6 vs 2.8, p=0.002) and more passes per coronary lesion (3.4 vs 1.7, p=0.001). Acute procedural revascularization results did not differ between groups. At 30 days, the major adverse event rate did not differ significantly between groups (32.9% of Impella patients vs 42.4% of IABP patients, p=0.078). At 90 days, Impella patients (39.5%) had a significantly lower major adverse event rate than IABP patients (51.0%; p=0.039). The 90-day event rates for the individual components of the composite major adverse event score differed only for severe hypotension requiring treatment, which was more common in patients treated with IABP (7.6% vs 2.4%, p=0.029).

In a post hoc analysis, results of the PROTECT II trial were reanalyzed by Dangas et al (2014), using a revised definition of MI in the determination of patients with major adverse events and major adverse cardiac and cerebral events. Unlike the original trial, which used a cutoff of 3 times the upper limit of normal for biomarker elevation to define periprocedural MI, the authors used a cutoff of 8 times the upper limit of normal for biomarker elevation or the presence of Q waves to define periprocedural MI. In multivariable analysis, compared with IABP, treatment with the Impella system was associated with freedom from 90-day major adverse events (OR=0.75; 95% CI, 0.61 to 0.92; p=0.007) and major adverse cardiac and cerebral events (OR=0.76; 95% CI, 0.61 to 0.96; p=0.020).

**Comparative Studies**

Reddy et al (2014) reported on outcomes for a series of 66 patients enrolled in a prospective, multicenter registry who underwent ventricular tachycardia (VT) ablation with a pVAD or IABP. Twenty-two patients underwent ablation with IABP assistance, while 44 underwent ablation with either the TandemHeart or Impella pVAD device (non-IABP group). Compared with patients who received support with an IABP, those who received support with a pVAD had more unstable VTs that could be mapped and ablated (1.05 vs 0.32, p<0.001), more VTs that could be terminated by ablation (1.59 vs 0.91, p=0.001), and fewer VTs terminated with rescue shocks (1.9 vs 3.0, p=0.049). More pVAD-supported patients could undergo entrainment/activation mapping (82% vs 59%, p=0.046). Mortality and VT recurrence did not differ over the study follow-up period (average, 12 months).

In a retrospective study, Aryana et al (2014) reported procedural and clinical outcomes for 68 consecutive unstable patients with scar-mediated epicardial or endocardial VT who underwent ablation with or without pVAD support. Thirty-four patients had hemodynamic support periprocedurally with a pVAD. Percutaneous VAD- and non-pVAD-supported patients were similar at baseline, with no differences in procedural success rates between groups. Compared with non-pVAD-supported patients, patients in the pVAD group had a longer maximum time in unstable VT (27.4 min vs 5.3 min, p<0.001), more VT ablations per procedure (1.2 vs 0.4, p<0.001), a shorter radiofrequency ablation time (53 seconds vs 68 seconds, p=0.022), and a shorter hospital length of stay (4.1 days vs 5.4 days, p=0.013). Over a follow-up of 19 months, rates of VT recurrence did not differ between groups.
Kovacic et al (2013) retrospectively compared outcomes for the TandemHeart and Impella devices in 68 patients undergoing high-risk PCI from 2005 to 2010 from a single-center database. There were no in-hospital deaths or strokes. There was 1 periprocedural myocardial infarction in the TandemHeart group and two in the Impella group. For patients with available intermediate and long-term data (n=63), there was not a statistically significant difference in time to death.

**Noncomparative Studies**

The PROTECT trial evaluated whether the Impella 2.5 system improves outcomes for patients undergoing high-risk PCI procedures. PROTECT 1 was a feasibility study of 20 patients who had left main disease or last patent coronary conduit that required revascularization but who were not candidates for coronary artery bypass graft surgery. High-risk PCI was performed using the Impella system for circulatory support. All procedures were completed successfully completed without any hemodynamic compromise in-procedure. Two (10%) patients died within 30 days and 2 (10%) patients had a periprocedural MI. Two other patients had evidence of hemolysis, which was transient and resolved without sequelae.

Schreiber et al (2017) reported outcomes for 127 consecutive patients from the USpella registry who were not in cardiogenic shock who underwent unprotected left main PCI supported with an Impella LV device between August 2008 and July 2015. The in-hospital and 30-day mortality rates were 1.6% and 2.4%, respectively. The 30-day major adverse cardiovascular event rate was 2.4%. One patient had vascular complications requiring surgery. Three (2.4%) patients had a hematoma, and 5 (3.9%) patients had bleeding requiring transfusion.

Sjauw et al. (2009) retrospectively analyzed 144 consecutive patients undergoing high-risk PCI with pVAD support (Impella system) from a European registry. End points included successful device function and incidence of adverse events at 30 days. The device was successfully implanted in all 144 patients. There was a periprocedural death and 8 deaths at 30 days for a mortality rate of 5.5%. Bleeding requiring transfusion or surgery occurred in 6.2% of patients, and vascular access site complications occurred in 4.0%. There was 1 (0.7%) stroke, and no MIs were reported.

Maini et al (2012) performed a similar retrospective analysis of 175 patients in the USpella registry undergoing high-risk PCI with pVAD support using the Impella 2.5 circulatory support system. The primary safety end point was the incidence of major adverse cardiac events at 30 days. Secondary end points included device safety and efficacy and patient outcomes at 30 days and 12 months. Angiographic revascularization was successful in 99% of patients. At 30-day follow up, the major adverse cardiac event rate was 8%; survival was 96%, 91%, and 88% at 30 days, 6 months, and 12 months, respectively. Secondary safety end points occurring most frequently included acute renal dysfunction (2.8%), hypotension on support (3.4%), VT, or cardiopulmonary resuscitation (2.8%); other vascular complications included vessel dissection and arteriovenous fistula (3.4%), hematomas ipsi- or contralateral to the device insertion site (8.6%), infection (5.1%), and blood transfusion (9.7%).
Other case series have described pVAD use in high-risk patients undergoing an invasive cardiac procedure, but given the lack of a comparator and the availability of higher quality data, these studies add little to the evidence base.

**pVADS as Bridge to Recovery for Cardiogenic Shock Refractory to IABP**

Case series of patients with cardiogenic shock refractory to IABP who were treated with pVAD have also been published. In the largest series, Kar et al. (2011) treated 117 patients who had severe, refractory cardiogenic shock with the TandemHeart System. Eighty patients had ischemic cardiomyopathy and 37 had nonischemic cardiomyopathy. There were significant improvements in all hemodynamic measures following LVAD placement. For example, the cardiac index increased from 0.52L/min/m² to 3.0L/min/m² (p<0.001), and systolic blood pressure increased from 75mm Hg to 100mm Hg (p<0.001). Complications were common after LVAD implantation. Thirty-four (29.1%) patients had bleeding around the cannula site, and 35 (29.9%) developed sepsis during the hospitalization. Groin hematoma occurred in 6 (5.1%) patients; limb ischemia in 4 (3.4%) patients; femoral artery dissection or perforation in 2 (1.7%) patients; stroke in 8 (6.8%) patients; and coagulopathy in 13 (11.0%) patients.

**Section Summary: Percutaneous Ventricular Assist Devices**

Percutaneous VADs have been tested in RCTs and uncontrolled studies of patients with cardiogenic shock, including those refractory to IABP, and in patients undergoing high-risk cardiac interventions such as PCI and VT ablation. The RCTs have not consistently reported a benefit for the use of pVADs. In addition, the RCTs and case series have reported high rates of adverse events that may outweigh any potential benefits. As a result, the evidence on pVADs does not demonstrate that use of pVADs is associated with improvements in health outcomes for patients with cardiogenic shock or for patients undergoing high-risk cardiac interventions.

**SUMMARY OF EVIDENCE**

**Ventricular Assist Device**

For individuals who have end-stage heart failure who receive a VAD as a bridge to transplant, the evidence includes single-arm trials and observational studies. Relevant outcomes are overall survival, symptoms, functional outcomes, quality of life (QOL), and treatment-related mortality and morbidity. There is a substantial body of evidence from clinical trials and observational studies supporting implantable VADs as a bridge to transplant in patients with end-stage heart failure, possibly improving mortality as well as QOL. These studies have reported that substantial numbers of patients have survived to transplant in situations in which survival would not be otherwise expected. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have end-stage heart failure who receive a VAD as destination therapy, the evidence includes a trial and multiple single-arm studies. Relevant outcomes are overall survival, symptoms, functional outcomes, QOL, and treatment-related mortality and morbidity. A well-designed trial, with 2 years of follow-up data, has demonstrated an advantage of implantable VADs
Implantable Ventricular Assist Devices and Total Artificial Hearts

as destination therapy for patients ineligible for heart transplant. Despite an increase in adverse events, both mortality and QOL appear to be improved for these patients. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Total Artificial Heart
For individuals who have end-stage heart failure who receive a TAH as a bridge to transplant, the evidence includes case series. Relevant outcomes are overall survival, symptoms, functional outcomes, QOL, and treatment-related mortality and morbidity. Compared with VADs, the evidence for TAHs in these settings is less robust. However, based on the lack of medical or surgical options for these patients and the evidence case series provide, TAH is likely to improve outcomes for a carefully selected population with end-stage biventricular heart failure awaiting transplant who are not appropriate candidates for a left VAD. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have end-stage heart failure who receive a TAH as destination therapy, the evidence includes 2 case series. Relevant outcomes are overall survival, symptoms, functional outcomes, QOL, and treatment-related mortality and morbidity. The body of evidence for TAHs as destination therapy is too limited to draw conclusions. The evidence is insufficient to determine the effects of the technology on health outcomes.

Percutaneous Ventricular Assist Device
For individuals with cardiogenic shock or who undergo high-risk cardiac procedures who receive a pVAD, the evidence includes randomized controlled trials. Relevant outcomes are overall survival, symptoms, morbid events, functional outcomes, QOL, and treatment-related mortality and morbidity. Four randomized controlled trials of pVAD vs IABP for patients in cardiogenic shock failed to demonstrate a mortality benefit and reported higher complication rates associated with pVAD use. Another randomized controlled trial comparing pVAD with IABP as an adjunct to high-risk percutaneous coronary interventions was terminated early due to futility; analysis of enrolled subjects did not demonstrate significant improvements in the pVAD group. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with cardiogenic shock refractory to IABP who receive a pVAD, the evidence includes case series. Relevant outcomes are overall survival, symptoms, morbid events, functional outcomes, QOL, and treatment-related mortality and morbidity. Case series of patients with cardiogenic shock refractory to IABP have reported improved hemodynamic parameters following pVAD placement. However, these uncontrolled series do not provide evidence that pVADs improve mortality, and high rates of complications have been reported with pVAD use. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

CLINICAL INPUT FROM PHYSICIAN SPECIALITY SOCIETIES AND ACADEMIC MEDICAL CENTERS
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 2 physician specialty societies and 5 academic medical centers while this policy was under review in 2014. Vetting focused on the use of percutaneous ventricular assist devices (pVADs) under the American Heart Association and American College of Cardiology guidelines (2013) and on the use of total artificial heart as destination therapy. All providing input supported the use of implantable ventricular assist devices as destination therapy subject to the guidelines in the policy statements. Most providing input considered total artificial hearts to be investigational for destination therapy; reviewers noted that there are limited clinical trial data to support the use of total artificial hearts as destination therapy.

Most providing input considered pVADs to be investigational as a “bridge to recovery” or “bridge to decision” and for all other indications. Some noted that pVADs may improve patients’ hemodynamics better than other alternatives, such as an intra-aortic balloon pump, but are associated with more complications. Some reviewers noted that, despite a lack of evidence to indicate that pVADs improve overall outcomes, there may be cases when pVADs may be considered to support an intervention or treatment for a life-threatening condition.

PRACTICE GUIDELINES AND POSITION STATEMENTS

Society for Cardiovascular Angiography and Interventions et al
In 2015, the Society for Cardiovascular Angiography and Interventions, the Heart Failure Society of America, the Society of Thoracic Surgeons, and the American College of Cardiology published a joint clinical expert consensus statement on the use of percutaneous mechanical circulatory support (MCS) devices in cardiovascular care. This statement addressed intra-aortic balloon pumps, left atrial-to-aorta assist device (eg, TandemHeart), left ventricle-to-aorta assist devices (eg, Impella), extracorporeal membrane oxygenation, and methods of right-sided support. Specific recommendations were not made, but the statement reviews the use of MCS in patients undergoing high-risk percutaneous intervention, those with cardiogenic shock, and those with acute decompensated heart failure.

American College of Cardiology Foundation and American Heart Association
The American College of Cardiology Foundation and American Heart Association (AHA) released guidelines for the management of heart failure in 2013 that included recommendations related to the use of MCS, including both durable and nondurable MCS devices. The guidelines categorized percutaneous ventricular assist devices (pVADs) and extracorporeal VADs as nondurable MCS devices. Table 6 provides class IIA guidelines on MCS devices.
Table 6. 2013 Guidelines on MCS

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COE</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>“MCS is beneficial in carefully selected patients with stage D HFrEF in whom definitive management (eg, cardiac transplantation) or cardiac recovery is anticipated or planned.”</td>
<td>IIA</td>
<td>B</td>
</tr>
<tr>
<td>“Nondurable MCS, including the use of percutaneous and extracorporeal ventricular assist devices (VADs), is reasonable as a “bridge to recovery” or “bridge to decision” for carefully selected patients with HFrEF with acute, profound hemodynamic compromise.”</td>
<td>IIA</td>
<td>B</td>
</tr>
<tr>
<td>“Durable MCS is reasonable to prolong survival for carefully selected patients with stage D HFrEF.”</td>
<td>IIA</td>
<td>B</td>
</tr>
</tbody>
</table>

**COE:** class of evidence; **HFrEF:** heart failure with reduced ejection fraction

These 2003 guidelines also noted:

“Although optimal patient selection for MCS remains an active area of investigation, general indications for referral for MCS therapy include patients with LVEF (left ventricular ejection fraction)<25% and NYHA (New York Heart Association) class III–IV functional status despite GDMT (guideline-directed medical therapy), including, when indicated, CRT (cardiac resynchronization therapy), with either high predicted 1- to 2-year mortality (eg, as suggested by markedly reduced peak oxygen consumption and clinical prognostic scores) or dependence on continuous parenteral inotropic support. Patient selection requires a multidisciplinary team of experienced advanced HF (heart failure) and transplantation cardiologists, cardiothoracic surgeons, nurses, and ideally, social workers and palliative care clinicians.”

In 2012, AHA published recommendations for the use of MCS. These guidelines defined nondurable MCS as intraballoon pumps, extracorporeal membrane oxygenation, extracorporeal VADs, and pVADs. Table 7 recommendations made on indications for the use of MCS, including durable and nondurable devices.

Table 7. 2012 Guidelines on MCS

<table>
<thead>
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<th>Recommendation</th>
<th>COE</th>
<th>LOE</th>
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<tr>
<td>“MCS for BTT indication should be considered for transplant-eligible patients with end-stage HF who are failing optimal medical, surgical, and/or device therapies and at high risk of dying before receiving a heart transplantation.”</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>“Implantation of MCS in patients before the development of advanced HF ... is associated with better outcomes. Therefore, early referral of HF patients is reasonable.”</td>
<td>IIA</td>
<td>B</td>
</tr>
<tr>
<td>“MCS with a durable, implantable device for permanent therapy or DT is beneficial for patients with advanced HF, high 1-year mortality resulting from HF, and the absence of other life-limiting organ dysfunction; who are failing medical, surgical, and/or device therapies; and who are ineligible for heart transplantation.”</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>“Elective rather than urgent implantation of DT can be beneficial when performed after optimization of medical therapy in advanced HF patients who are failing medical, surgical, and/or device therapies.”</td>
<td>IIA</td>
<td>C</td>
</tr>
<tr>
<td>“Urgent nondurable MCS is reasonable in hemodynamically compromised HF patients with end-organ dysfunction and/or relative contraindications to heart transplantation/durable MCS that are expected to improve with time and restoration of an improved hemodynamic profile.”</td>
<td>IIA</td>
<td>C</td>
</tr>
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</table>
“These patients should be referred to a center with expertise in the management of durable MCS and patients with advanced HF.”

“Patients who are ineligible for heart transplantation because of pulmonary hypertension related to HF alone should be considered for bridge to potential transplant eligibility with durable, long-term MCS.”

Heart Failure Society of America

Heart Failure Society of America published guidelines in 2010 on surgical approaches to the treatment of heart failure. Table 8 lists recommendations on left VADs.

Table 8. Guidelines on Left Ventricular Assist Devices

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>SOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients awaiting heart transplantation who have become refractory to all means of medical circulatory support should be considered for a mechanical support device as a bridge to transplant.”</td>
<td>B</td>
</tr>
<tr>
<td>“Permanent mechanical assistance using an implantable assist device may be considered in highly selected patients with severe HF refractory to conventional therapy who are not candidates for heart transplantation, particularly those who cannot be weaned from intravenous inotropic support at an experienced HF center.”</td>
<td>B</td>
</tr>
<tr>
<td>“Patients with refractory HF and hemodynamic instability, and/or compromised end-organ function, with relative contraindications to cardiac transplantation or permanent mechanical circulatory assistance expected to improve with time or restoration of an improved hemodynamic profile should be considered for urgent mechanical circulatory support as a ‘bridge to decision.’ These patients should be referred to a center with expertise in the management of patients with advanced HF.”</td>
<td>C</td>
</tr>
</tbody>
</table>

HF: heart failure; SOE: strength of evidence.

European Society of Cardiology

In 2016, the European Society of Cardiology issued guidelines on the diagnosis and treatment of acute and chronic heart failure, which updated its guidelines published in 2008, 2010, and 2012. These 2016 guidelines made the following recommendations on VADs (see Table 9).

Table 9. Guidelines on Left Ventricular Assist Devices

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COE</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVAD should be considered as a bridge to transplant in refractory heart failure</td>
<td>IIA</td>
<td>C</td>
</tr>
<tr>
<td>LVAD should be considered as destination therapy in refractory heart failure</td>
<td>IIA</td>
<td>B</td>
</tr>
</tbody>
</table>

COE: class of evidence; LOE: level of evidence; LVAD: left ventricular assist device.
The guidelines also stated that “...temporary percutaneous MCS cannot be recommended as a proven or efficacious treatment for acute cardiogenic shock. In selected patients it may serve as a bridge to definite therapy.”

**International Society for Heart and Lung Transplantation**
The 2013 guidelines on MCS by the International Society for Heart and Lung Transplantation recommended that, for patients with decompensated heart failure, “Short term mechanical support, including extracorporeal membrane oxygenation should be used in acutely decompensated patients who are failing maximal medical therapy” (level of evidence: C). The guidelines also stated that “use of temporary mechanical support should be strongly considered in patients with multiorgan failure, sepsis, or on mechanical ventilation to allow for successful optimization of clinical status and neurologic assessment prior to placement of a long-term MCSD [mechanical circulatory support device]” (level of evidence: C).

**Medicare National Coverage**
Medicare has a national coverage determination (NCD) for artificial hearts and related devices, including VADs. The NCD mandates coverage for VADs in the *postcardiotomy setting* as long as the following conditions are met:

- The VAD has “approval from the Food and Drug Administration (FDA)” for post-cardiotomy support.
- The VAD is “used according to the FDA-approved labeling instructions”.

The NCD national coverage policy also mandates coverage for VADs as a *bridge-to-transplant* as long as the following conditions are met:

- The VAD has approval from FDA for the bridge-to-transplant indication.
- The VAD is “used according to the FDA-approved labeling instructions.”
- “The patient is approved for heart transplantation by a Medicare-approved heart transplant center...”
- “The implanting site, if different than the Medicare-approved transplant center, must receive written permission from the Medicare-approved heart transplant center under which the patient is listed prior to implantation of the VAD.”

The NCD mandates coverage for VADs as *destination therapy* as long as the following conditions are met:

- The VAD has approval from FDA for the destination therapy indication.
- Patient selection:
  - New York Heart Association Class IV end-stage left ventricular failure
  - Not candidates for heart transplantation,
  - Failed to respond to optimal medical management,
  - Left ventricular ejection fraction (LVEF) <25%, and,
  - Demonstrated functional limitation
Beneficiaries receiving VADs for DT must be managed by an explicitly identified cohesive, multidisciplinary team of medical professionals with the appropriate qualifications, training, and experience... The team members must be based at the facility and must include individuals with experience working with patients before and after placement of a VAD.

Facilities must be credentialed by an organization approved by the Centers for Medicare & Medicaid Services.”

The NCD mandates coverage for artificial hearts as bridge to transplant or destination therapy when performed under coverage with evidence development when a clinical study meets the criteria outlined in the Medicare policy.

VII. Important Reminder
The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 10.

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
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<td>Ongoing</td>
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<tr>
<td>NCT02326402</td>
<td>THEME Registry: TandemHeart Experiences and Methods</td>
<td>200</td>
<td>Dec 2017</td>
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<tr>
<td>NCT01774656a</td>
<td>Remission From Stage D Heart Failure (RESTAGE-HF)</td>
<td>40</td>
<td>Dec 2017</td>
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<tr>
<td>NCT01627821a</td>
<td>Evaluation of the Jarvik 2000 Left Ventricular Assist</td>
<td>350</td>
<td>Dec 2018</td>
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<tr>
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<td>Study Title</td>
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<td>Start Date</td>
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<td>---------------------------------------------------------------------------------------------------</td>
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<tr>
<td>NCT01369407</td>
<td>REVIVE-IT Registry (REVIVAL: Registry Evaluation of Vital Information For VADs in Ambulatory Life)</td>
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<td>Jun 2019</td>
</tr>
<tr>
<td>NCT02459054</td>
<td>SynCardia 50cc Temporary Total Artificial Heart (TAH-t) as a Bridge to Transplant</td>
<td>72</td>
<td>Jun 2020</td>
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<td>NCT02232659</td>
<td>SynCardia 70cc Temporary Total Artificial Heart (TAH-t) for Destination Therapy (DT)</td>
<td>38</td>
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<td>NCT02387112</td>
<td>Early Versus Emergency Left Ventricular Assist Device Implantation in Patients Awaiting Cardiac Transplantation</td>
<td>500</td>
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<td>NCT01966458a</td>
<td>A Prospective, Randomized, Controlled, Unblinded, Multi-Center Clinical Trial to Evaluate the HeartWare® Ventricular Assist Device System for Destination Therapy of Advanced Heart Failure</td>
<td>465</td>
<td>Aug 2016</td>
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<td>NCT01187368a</td>
<td>A Prospective Study to Evaluate the Safety and Efficacy of the EVAHEART LVAS for Use as a Bridge-to-Transplant</td>
<td>20</td>
<td>Jun 2017 (suspended)</td>
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<td>NCT02468778</td>
<td>Supporting Patients Undergoing High-Risk PCI Using a High-Flow PERcutaneous Left Ventricular Support Device (SHIELD II)</td>
<td>425</td>
<td>Jan 2018 (suspended)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.

VIII. References
31. Dickstein K, Cohen-Solal A, Filippatos G et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). European heart journal 2008; 29(19):2388-442.
41. TEC Assessment Program 2002. Left ventricular assist devices as destination therapy for end-stage heart failure. Volume 17, Tab 19
44. Long JW, Kfoury AG, Slaughter MS et al. Long-term destination therapy with the HeartMate XVE left ventricular assist device: improved outcomes since the REMATCH study. Congest Heart Fail 2005; 11(3):133-138


91. Peura JL, Colvin-Adams M, Francis GS et al. Recommendations for the use of mechanical circulatory support: device strategies and patient selection: a scientific statement from the


