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**Medical Policy Manual**

**Topic:** Ventricular Assist Devices and Total Artificial Hearts

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**Section:** Surgery

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**IMPORTANT REMINDER**

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

## DESCRIPTION

Ventricular assist devices and total artificial hearts provide mechanical circulation for patients with end-stage heart disease who are waiting for, or cannot survive, a heart transplant.

### Background

### Ventricular Assist Devices (VADs)

Biventricular Right Ventricular and Left Ventricular Devices

There are three kinds of ventricular assist devices: biventricular (BiVADs), right ventricular (RVAD), and left ventricular (LVADs). Surgically implanted ventricular assist devices (VADs) are attached to the native heart and vessels to provide temporary mechanical circulatory support by augmenting cardiac output. LVADs to support the left ventricle are the most commonly used VADs, but right ventricular and biventricular devices may also be used. LVADs are most commonly used as a bridge to transplantation for those patients who are not expected to survive without mechanical support until a heart becomes available. LVADs may also be used as a bridge to recovery in patients with reversible conditions affecting cardiac output (e.g., post-cardiotomy cardiogenic shock). More recently, given the success of LVADs for prolonged periods of time, there has been interest in using LVADs as permanent "destination" therapy for patients with end-stage heart disease who are not candidates for human heart transplantation due to age or other comorbidities.

Percutaneous Ventricular Assist Devices

Percutaneous Ventricular Assist Devices (pVADS), also known as circulatory assist devices, have been developed for short-term use in patients who require acute circulatory support. These devices are placed through the femoral artery. Two different pVADs have been developed, the TandemHeart™ (Cardiac Assist™), and the Impella® device (AbioMed™). 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 introduced through a femoral artery catheter. In this device, a small pump is contained within the catheter that is 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 (MI), stroke, and arrhythmias. There are several situations in which pVADs may offer possible benefits:

- Cardiogenic shock that is refractory to medications and intra-aortic balloon pump (IABP)
- Cardiogenic shock, as an alternative to IABP
- High-risk patients undergoing invasive cardiac procedures who need circulatory support.

## Total Artificial Hearts

The total artificial heart (TAHs) replaces the native ventricles and is attached to the pulmonary artery and aorta; the native heart is typically removed. TAHs may be implanted temporarily as a bridge to heart transplantation or permanently as destination therapy in those who are not candidates for transplantation.

The CardioWest™ Total Artificial Heart is a temporary TAH, which is used in the inpatient hospital setting as a bridge to heart transplantation. The CardioWest TAH is implanted after the native ventricles have been excised. The AbioCor® Implantable Replacement Heart is a permanent TAH currently available as destination therapy for people who are not eligible for a heart transplant and who are unlikely to live more than a month without intervention. The device has an internal battery that allows the recipient to be free from all external connections for up to one hour. The system also includes two external batteries that allow free movement for up to two hours. During sleep and while batteries are being recharged, the system can be plugged into an electrical outlet. In order to receive the AbioCor artificial heart, in addition to meeting other criteria, patients must undergo a screening process to determine if their chest volume is large enough to hold the two-pound device which is too large for about 90% of women and many men.

## Regulatory Status

| Device Name | Device Type | Manufacturer | FDA Approval | Indication |
|---|---|---|---|---|
| HeartMate II® | LVAD | Thoratec Corp. | PMA | Bridge to transplant and destination therapy |
| Thoratec® IVAD | BiVAD | Thoratec Corp. | PMA + Supplement | Bridge to transplant and post-cardiotomy |
| Levitronix Centrimag® | RVAD | Levitronix, LLC | HDE | Postcardiotomy (temporary circulatory support for up to 14 days) |
| Novacor® | LVAD | World Heart, Inc. | PMA | Bridge to transplant |
| DeBakey VAD® Child | LVAD | MicroMed Technology, | HDE | Bridge to transplant in |

| | | | | |
|---|---|---|---|---|
| | | Inc. | | children 5-16 years of age |
| EXCOR® Pediatric System | BiVAD | Berlin Heart, Inc. | HDE | Bridge to transplant, pediatric (newborns to teens) |
| Jarvik 2000 | LVAD | Jarvik Heart, Inc. | *IDE-Investigational*† | |
| HeartWare® Ventricular Assist System (HVAD®) | VAD | Heartware Intl., Inc. | PMA | Bridge to transplant – for use in-hospital or out-of-hospital |
| Impella® Recover LP 2.5 | pVAD | Abiomed, Inc. | 510(k) | Partial circulatory support using an extracorporeal bypass control unit for periods up to 6 hours |
| TandemHeart® | pVAD | CardiacAssist, Inc. | 510(k) | Temporary left ventricular bypass of six hours of less |
| SynCardia Temporary TAH (formerly called CardioWest™) | Temporary total artificial heart | SynCardia Systems, Inc. | 510(k) | Bridge to transplant – for use inside the hospital |
| AbioCor® TAH | Implantable Replacement Heart System | AbioMed, Inc. | HDE | Destination therapy |

†FDA Investigational Device Exemption (IDE) is not considered a full FDA approval. Devices with an IDE designation are considered investigational.

In August 2015, the U.S. Food and Drug Administration (FDA) published a safety communication about serious adverse events with implantable left ventricular assist devices.[1] The warning reports:

- Up to 8.4% of patients using the Thoratect HeartMate II have experienced pump thrombosis at three months;
- Up to 28.7% of patients using the HeartWave HVAD have experience one or more strokes over two years; and
- The FDA is aware of bleeding complications related to both the Thoratec HeartMate II and HeartWave HVAD.

Although adverse events have been reported, the FDA recognizes "that LVADs are life-sustaining, life-saving devices for patients with advanced left ventricular heart failure. When used for the currently approved indications in appropriately selected patients, we believe the benefits of these LVADs continue to outweigh the risks"

## MEDICAL POLICY CRITERIA

I. Implantable ventricular assist devices (i.e., LVADs, RVADs and BiVADs)

A. Implantable ventricular assist devices with FDA PMA, 510(k), or HDE clearance may be considered **medically necessary** for any of the following indications (1-3):

1. As a bridge to transplantation for patients who meet all of the following criteria:

a. Currently listed as a heart transplantation candidate or undergoing evaluation to determine candidacy for heart transplantation

b. Not expected to survive until a donor heart can be obtained

2. For use in the post-cardiotomy setting in patients who are unable to be weaned off cardiopulmonary bypass.

3. As destination therapy in patients meeting all of the following criteria:

a. End-stage heart failure

b. Documented ineligibility for human heart transplantation

c. One of the following criteria is met:

i. New York Heart Association (NYHA) class III or IV* for at least 28 days who have received at least 14 days support with an intraaortic balloon pump or are dependent on intravenous inotropic agents, with two failed weaning attempts

ii. NYHA class IV* heart failure for at least 60 days.

* NYHA Class III = marked limitation of physical activity; less than ordinary activity leads to symptoms

NYHA Class IV = inability to carry on any activity without symptoms; symptoms may be present at rest

B. Ventricular assist devices are considered **investigational** in all other circumstances, including but not limited to the following:

1. Use of a non-FDA approved ventricular assist device.

2. Percutaneous ventricular assist devices (pVADs)

II. Total Artificial Hearts

A. Total artificial hearts with FDA PMA, 510(k), or HDE clearance may be considered **medically necessary** as a bridge to heart transplantation in patients meeting all of the following criteria:

1. Has biventricular failure

2. Currently listed as heart transplantation candidate or undergoing evaluation to determine candidacy for heart transplantation

3. Not considered a candidate for a univentricular or biventricular support device

4. Have no other reasonable medical or surgical treatment options

5. Not expected to survive until a donor heart can be obtained

B. Total artificial hearts are considered **investigational** in all other circumstances, including but not limited to the following:

1. Use as destination therapy

2. Use of a total artificial heart that does not have FDA PMA, 510(k), or HDE clearance

## SCIENTIFIC EVIDENCE

The principal outcome associated with treatment of refractory heart failure (HF) is to prolong survival, either temporarily as a bridge to decision, recovery, or heart transplantation, or permanently as a replacement for the damaged heart in patients who are not candidates for heart transplantation.

### Ventricular Assist Devices

Bridge to Transplantation, Left Ventricular Assist Devices

*Systematic Review*

A systematic review published in 2011 supported the conclusions reached in the 1996 BCBSA TEC assessment.[2,3] The 2011 review included 31 observational studies that compared outcomes of transplant in patients who did and did not have pre-transplant left ventricular assist devices (LVADs). Survival at one year was more likely in patients who had LVAD treatment, but this benefit was confined to patients who received an intra-corporeal device (relative risk [RR]: 1.8, 95% confidence interval [CI]: 1.53-2.13). For patients treated with an extracorporeal device, the likelihood of survival was not different from patients who were not treated with an LVAD (RR: 1.08, 95% CI: 0.95-1.22). There was no difference in the risk of rejection between patients who did and did not receive LVAD treatment.

*Nonrandomized Studies*

Adult patients

Additional reports not included in the 1996 TEC assessment or the 2011 systematic review are consistent with the above analysis.[4-6] It should be recognized that left ventricular assist devices cannot change the number of patients undergoing heart transplantation due to the fixed number of donor hearts. However, the LVAD will categorize its recipient as a high priority heart transplant candidate. Currently available LVADs consist of pulsatile devices that require both stiff power vent lines that perforate the skin and bulky implantable pump chambers. There is considerable research interest in developing non-pulsatile axial flow systems that have the potential for small size and low-noise levels.[7-12]

In 2014, Deo et al reported no significant differences in outcomes for 37 patients bridged to transplant with a ventricular assisted device (VAD) and 70 patients who underwent a heart transplant directly.[13] In 2013, Slaughter et al. reported combined outcomes for patients included in the HeartWare® bridge-to-transplant study.[14] 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 days of follow-up at the time of this 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 quality of life measures.

In 2012, Aaronson et al. reported results of a multicenter, prospective study of a newer generation LVAD, the HeartWare®, which is a smaller, continuous flow centrifugal device that is implanted in the pericardial space.[15] The study enrolled 140 patients who were awaiting heart transplantation who underwent HeartWare® implantation. A control group of 499 subjects was comprised of patients drawn from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) database, which collects data on patients who receive FDA-approved durable mechanical circulatory support 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, and adverse event outcomes in the HeartWare® group. Success 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.

Evidence suggests that the HeartMate II axial achieves similar or better results than the earlier pulsatile HeartMate I model. In six reports with samples ranging from 32 to 279 patients, most participants received the new device as a bridge to transplantation.[16-21] Survival rates at six months and one year were 67-87%, and 50-80%, respectively. These rates are similar to those reported from INTERMACS.[22] An additional report from INTERMACS comparing the HeartMate II to other LVAD devices for patients who received them with a bridge to transplantation indication reported that 80% and 91% of HeartMate II and other LVAD patients reached transplant, cardiac recovery, or ongoing LVAD support by six months.[23] One report, however, compared HeartMate I and HeartMate II recipients at a single center, finding the same one year survival and similar rates of subsequent development of right heart failure.[18] Serious adverse events occurring after HeartMate II implantation included bleeding episodes requiring reoperation, stroke, infection, and device failure. A European study that included 67 bridge to transplant patients and 31 destination therapy patients found similar one year survival rates in the two groups: 63% and 69%, respectively.

Pediatric Patients

Publications on children using VADs as a bridge to transplantation have reported positive outcomes. For example, Davies et al reported that pediatric patients requiring a pretransplantation VAD had similar long-term survival to those not receiving mechanical circulatory support.[24] In 2013, Almond et al. reported results from a prospective, multicenter registry to evaluate outcomes in children who received the Berlin Heart EXCOR device as a bridge to transplant.[25] All patients were followed up 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% alive with the device in place. In a follow-up study which 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.[26]

Section Summary

In adults, the evidence on the efficacy of LVADs as bridge to transplant consists of numerous nonrandomized studies comparing different LVADs devices among patients who have no other treatment options. In children, the evidence consists of several nonrandomized studies. These studies report that substantial numbers of patients survive the transplant in situations in which survival would not be otherwise expected. Despite the lack of high-quality studies, this evidence is sufficient to determine that outcomes are improved in patients who have no other options for survival.

Ventricular Assist Devices as Bridge to Recovery

*Nonrandomized Studies*

Support from VADs was originally indicated for the treatment of postcardiotomy cardiogenic shock in patients who could not be weaned from cardiopulmonary bypass. VAD use in this setting is temporary and brief, lasting between 1.4 and 5.7 days. The overall salvage rate for this indication is low, at approximately 25%; however, without VAD support, patients with refractory postcardiotomy cardiogenic shock would experience 100% mortality.[6,27,28]

In 2014, Takayama et al reported outcomes for a retrospectively defined cohort of 143 patients who received a CentriMag VAD as a "bridge to decision" for refractory cardiogenic shock due to a variety of causes.[29] 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 post-heart transplantation (n=2), and right ventricular failure post-implantable LVAD (n=13). The device configuration was biventricular in 67%, isolated right VAD in 26%, and isolated left VAD 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 transplantation.

In a smaller single-center retrospective cohort study, Mohamedali et al 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 (VA) extracorporeal membrane oxygenation (ECMO), while the remainder received just biventricular VAD support.[30] Overall, 23 patients were explanted, nine to recovery, 14 to a durable LVAD, with three additional patients explanted for withdrawal of care. However, given that the study included patients who received VA ECMO, it is difficult to assess the relative impact of VAD support alone.

Six studies using the Centrimag RVAD included between 12 and 32 patients, the majority of whom received biventricular devices.[28,31-35] Indications and numbers of patients in these five studies were: support for post-cardiotomy cardiogenic shock (bridge to recovery), bridge to long-term device implantation (n=9), treatment of right heart failure in patients who previously received LVADs, bridge to later decision when neurologic status is clarified, and acute donor graft failure. The mean time on mechanical circulatory support ranged from 9.4 days to 46.9 days. The 30-day mortality rates were between 17% and 63%. The proportion of patients discharged from the hospital was between 30% and 83%. Major complications included bleeding requiring reoperation, sepsis, and stroke. No device failures were observed in these studies.

In a prospective multicenter study to assess myocardial recovery in patients with LVAD implantation as a bridge to transplant, Maybaum et al. evaluated 67 patients with heart failure who had undergone LVAD implantation for severe heart failure.[36] After 30 days, patients demonstrated significant improvements compared with pre-LVAD state in left ventricular ejection fraction (LVEF, 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, $p<0.001$). However, only 9% of patients demonstrated enough recovery to have their LVAD explanted.

In a 2006 study, a series of 15 patients with severe heart failure due to nonischemic cardiomyopathy underwent implantation of LVADs, along with medical management designed to enhance myocardial recovery.[37] Eleven of 15 patients had enough myocardial recovery to undergo LVAD explantation; two patients died after explantation. Among those who survived, the cumulate rate of freedom from recurring heart failure was 100% and 88.9%, respectively, at one and four years post explantation. 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.[38] They included 20 patients who received a combination of angiotensin converting enzyme ACE inhibitors, beta blockers, and adosterol antagonists followed by the β2-agonist clenbuterol. One patient was lost to follow-up and 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 one and three years.

*Section Summary*

The studies previously outlined indicate that a subset of patients who receive a VAD as a bridge to transplant demonstrate 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. Finally, current evidence is insufficient to allow the identification of other heart failure patient populations who might benefit from the use of a VAD as a specific bridge-to-recovery treatment strategy. Ongoing research studies are addressing this question, along with protocols for transitioning patients off VAD use.

Left Ventricular Assist Devices as Destination Therapy

*Technology Assessment*

The policy statement regarding LVADs as destination therapy was initially based on a 2002 TEC assessment[39] 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.[40] The study was a cooperative effort of Thoratec, Columbia University and the National Institutes of Health.

- The randomized trial found that patients with end-stage heart failure who are not candidates for cardiac transplantation have significantly better survival on an LVAD compared with treatment by optimal medical therapy. Median survival was improved by approximately 8.5 months. Serious adverse events were more common in the LVAD group, but these appear to be outweighed by this group's better outcomes on function. NYHA Class was significantly improved, as was quality of life among those living to 12 months.

- LVAD 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.

*Randomized Studies*

Park et al published a further follow-up of patients in the REMATCH trial, mentioned in the above TEC assessment, which found that survival and quality of life benefits were still apparent with extended two year follow-up.[41]

*Nonrandomized Studies*

In 2014 Jorde et al published results from an FDA-required postapproval study of the HeartMate II device for destination therapy.[42] The study 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 treated in the original trial, which compared patients who received the HeartMate II to earlier generation devices (Slaughter et al [2009], described below).[43] Survival in the postapproval cohort was 82% and 69% at one and two years postoperatively, respectively.

In addition, other case series suggest continuing improvement in outcomes related to ongoing improvements in the device and in patient management.[44] However, the durability of the HeartMate device used in the REMATCH trial is a concern; for example, at one participating institution, all six long-term survivors required device change-outs. Next generation devices consisting of smaller continuous flow devices are eagerly anticipated.

*Section Summary*

The primary evidence on the efficacy of LVADs as destination therapy in patients who are not transplant candidates is from the REMATCH study. This study reported that the use of LVADs led to improvements in survival, quality of life, and functional status.

Percutaneous Ventricular Assist Devices

*Alternative to Intra-Aortic Balloon Pump in Cardiogenic Shock*

Systematic Review

A systematic review and meta-analysis of three trials was published in 2009.[45] The meta-analysis by Chen et al., included a total of 100 patients, 53 treated with a pVAD and 47 treated with an IABP. All three study populations included patients with acute MI and cardiovascular shock; one of the trials[46] restricted this population to patients who were post-revascularization in the acute MI setting. The primary outcomes reported were 30-day mortality, hemodynamic measures of LV pump function, and adverse events.

Randomized Controlled Trials

The three randomized controlled trials (RCTs), as mentioned above in the systematic review, compared percutaneous ventricular assist devices (pVAD) to intra-aortic balloon pump (IABP) in patients with cardiogenic shock.[46-48] None of the three trials reported an improvement in mortality associated with pVAD use. The combined analysis estimated the relative risk for death in pVAD patients as 1.06 (95% CI 0.68-1.66, p=0.80). All three trials reported an improvement in LV hemodynamics in the pVAD group. On combined analysis, there was a mean increase in cardiac index of 0.35 L/min/m2 for the pVAD group, an increase in mean arterial pressure of 12.8mm Hg (95% CI 3.6-22.0, p<0.001), and a decrease in pulmonary capillary wedge pressure of 5.3mm Hg (95% CI 1.2-9.4, 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 with a relative risk of 2.35 (95% CI 1.40-3.93). Leg ischemia was also more common in the pVAD group, but this difference did not meet statistical significance (relative risk [RR] 2.59, 95% CI 0.75-8.97, p=0.13).

Nonrandomized studies

In 2014, O'Neill et al compared outcomes for patients with acute MI complicated by cardiogenic shock who received pVAD support pre-PCI with those who received pVAD support post-PCI using data from

154 consecutive patients enrolled in a multicenter registry.[49] Patients who received pVAD support pre-PCI had higher survival to discharge compared with those who received pVAD support post-PCI (65.1% vs 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.

Published case series and registry data have reported high success rates with pVAD as an alternative to IABP as a bridge to alternative therapies.[50-52] However, given the availability of RCT evidence, these studies add a limited amount to the body of evidence on the efficacy of the pVADs for the management of cardiogenic shock.

*Bridge to Recovery in Cardiogenic Shock Refractory to Intra-Aortic Balloon Pump*

Nonrandomized studies

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. treated 117 patients who had severe, refractory cardiogenic shock with the TandemHeart® System.[53] Eighty patients had ischemic cardiomyopathy and 37 had nonischemic cardiomyopathy. There were significant improvements in all hemodynamic measures following LVAD placement. For example, cardiac index increased from 0.52+0.8L/min/m2 to 3.0+0.9L/min/m2 ($p<0.001$) and the systolic BP increased from 75+15mm Hg to 100+15mm Hg ($p<0.001$). Complications were common post LVAD implantation. Thirty-four patients had bleeding around the cannula site (29.1%) and 35 developed sepsis during the hospitalization (29.9%). Groin hematoma occurred in 6 patients (5.1%); limb ischemia in four patients (3.4%); femoral artery dissection or perforation in two patients (1.7%); stroke in eight patients (6.8%); coagulopathy in 13 patients (11.0%).

*High-Risk Patients Undergoing Invasive Cardiovascular Procedures*

Randomized Controlled Trials

The PROTECT trial intended to evaluate whether the Impella® 2.5 system improved outcomes for patients undergoing high-risk percutaneous coronary intervention (PCI) procedures.[54] PROTECT I 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 (CABG) surgery. High-risk PCI was performed using the Impella® system for circulatory support. All of the procedures were completed successfully without any hemodynamic compromise during the procedures. There were two patient deaths within 30 days (10%) and two patients had a periprocedural MI (10%). An additional two patients had evidence of hemolysis, which was transient and resolved without sequelae.

The PROTECT II trial was planned as an RCT to compare the Impella® system with IABP in patients undergoing high-risk PCI procedures. Enrollment was planned for 654 patients from 50 clinical centers. The primary end-point was the composite of 10 different complications occurring within 30 days of the procedure, with the authors 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 of the 452 patients enrolled revealed that the primary endpoint could not be reached. At this point, approximately half the planned patients had been enrolled. Results were published by O'Neill et al. in 2012.[55] The study's primary analysis was intention to treat, and included all 448 patients randomly assigned to the Impella® system (N=225) or IABP (N=223). The primary composite endpoint of major adverse effects 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 MI between the Impella® patients and the IABP patients.

In a post-hoc analysis, results of the PROTECT II trial were reanalyzed by Dangas et al, using a revised definition of MI in the determination of patients with major adverse events and major adverse cardiac and cerebral events.[56] In contrast to the original trial, which used a cutoff of three times the upper limit of normal for biomarker elevation to define periprocedural MI, the authors used a cutoff of eight 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).

In 2015, Kovacic et al published results from a sub-study of a prespecified subgroup analysis of the PROTECT II trial, which compared outcomes for the Impella system compared with IABP among 325 patients with 3-vessel disease with LVEF less than or equal to 30%.[57] 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 had a significantly lower major adverse event rate compared with IABP patients (39.5% vs 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).

Nonrandomized Studies

Reddy et al reported outcomes for a series of 66 patients enrolled in a prospective, multicenter registry who underwent ventricular tachycardia ablation with a pVAD or IABP.[58] 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 greater numbers of unstable ventricular tachycardias that could be mapped an ablated (1.05 vs 0.32, p<0.001), greater numbers of ventricular tachycardias that could be terminated by ablation (1.59 vs 0.91, p=0.001), and fewer numbers of ventricular tachycardias that were 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 ventricular tachycardia recurrence did not differ over the study follow up period, which averaged 12 months.

In a retrospective study, Aryana et al reported procedural and clinical outcomes for 68 consecutive unstable patients with scar-mediated epicardial or endocardial ventricular tachycardia who underwent ablation with or without pVAD support.[59] Thirty-four patients had hemodynamic support periprocedurally with a pVAD. pVAD- 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 ventricular tachycardia (27.4 vs 5.3 minutes, p<0.001), a greater number of ventricular tachycardia ablations per procedure (1.2 vs 0.4, p<0.001), a shorter radiofrequency ablation time (53 vs 68 seconds, p=0.022), and a shorter hospital length of stay (4.1 vs 5.4 days, p=0.013). Over a follow up period of 19 months, rates of ventricular tachycardia recurrence did not differ between groups.

Other studies are limited to case series [60,61], registry data [62], and a retrospective analysis.[63,64] While these studies have reported feasibility and promising outcomes for this use of pVADs, randomized comparative trials are needed to validate these results.

Section Summary

pVADs have been tested in randomized controlled trials (RCts) and nonrandomized studies of patients with cardiogenic shock and in patients undergoing high-risk cardiac interventions. The RCTs do not consistently report a benefit for use of pVADs. In addition, both the RCTs and nonrandomized studies report high rates of adverse events that may outweigh any potential benefits. As a result, the evidence on pVADs does not support demonstrate that pVADs are associated with an improvements in health outcomes for patients with cardiogenic shock or in patients undergoing high-risk cardiac interventions.

Continuous Flow versus Pulsatile Flow Ventricular Assist Devices

*Randomized Controlled Trials*

In December 2009, Slaughter et al published data from an unblinded randomized multicenter trial.[43] Subjects were randomized to continuous-flow or pulsatile-flow devices on a 2:1 block-randomization basis. The primary outcome measured was a composite endpoint of 2-year survival, free of disabling stroke or need for device replacement. Continuous-flow patients (n=134) reached the primary outcome at a rate of 46% (95% confidence interval [CI] 38-55) compared to pulsatile-flow patients (n=66) rate of 11% (95% CI 3-18), which was a significant difference ($p<0.001$). 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 endpoint; two year death rate also favored this device (58% vs. 24%, $p=0.008$). Stroke and death (within two years of implantation) were similar in the two groups (stroke rate 12% and death rate 36%). Quality of life scores were also similar in the two groups. Although unblinded, this randomized trial adds to the evidence favoring continuous-flow devices.

*Nonrandomized Studies*

Dell'Aquila et al compared outcomes for patients treated with a third-generation continuous flow device, the HeartWare device, with those for patients treated with earlier generation devices in a single-center study.[65] Comparison-group patients received either an earlier generation continuous flow device or a pulsatile flow device. Of 287 patients who received VAD support from 1993 to 2012, 52 received a HeartWare device, 76 an earlier generation continuous flow device, and 159 a pulsatile device. Survival was significantly better for patients who received a third-generation device, with 24 months survival of 70.4%, compared with 33.7% for patients who received an earlier generation continuous flow device and 33.8% for patients who received a pulsatile flow device ($p=0.013$). The difference in survival associated with third generation devices was more pronounced for higher scores on the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACs) scale.

Nativi et al. published a non-randomized comparison of pulsatile versus continuous flow devices using data from the registry of the International Society for Heart and Lung Transplantation on 8,557 patients undergoing transplant.[66] Comparisons were made among patients receiving a pulsatile LVAD, a continuous flow LVAD, and no LVAD. Two time periods were used for analysis, the first was pre-2004, when nearly all LVADs were pulsatile devices, and post-2004 when continuous use devices began to be used in clinical care. Comparing the first time period to the second time period, there was a significantly greater risk of mortality in the first time period compared to the second time period (relative risk [RR]: 1.30, 95% CI 1.03-1.65, $p=0.03$). When analysis was confined to the second time

period, there was no significant improvement in survival for the continuous group compared to the pulsatile group (RR: 1.25, 95% CI: 1.03-1.65, p=0.03).

Other non-randomized studies that have compared outcomes from different types of LVADs have been smaller and/or focused on physiologic outcomes.[67-70] In some of these studies, the continuous flow devices exhibit greater improvement in physiologic measures, but none of these studies have reported significant differences between devices in clinical outcomes.

*Section Summary*

The evidence on the comparative efficacy of different devices consists of one 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 one database study with large numbers of patients, have not reported differences between devices on clinical outcomes.

Clinical Practice Guidelines for Ventricular Assist Devices

*American College of Cardiology Foundation/American Heart Association (ACCF/AHA)*[71]

The 2013 ACCF/AHA practice guidelines for the management of heart failure included the recommendations below related to mechanical circulatory support (MCS) which includes LVADs. All of these recommendations were rated II.a., level of evidence B, defined as a recommendation in favor of the treatment being useful, with some conflicting evidence from a single RCT or nonrandomized studies.

- MCS is considered beneficial in carefully selected patients with stage D heart failure with reduced ejection fraction (HFrEF) as a bridge to transplantation or recovery.
- Nondurable mechanical cardiac support including percutaneous and extracorporeal VADs are considered "reasonable" as a bridge to recovery or a bridge to decision for carefully selected patients with HFrEF with acute, profound hemodynamic compromise.
- Durable (permanent) MCS is considered reasonable to prolong survival for carefully selected patients with stage D HFrEF.

The guidelines note that, although optimal patient selection for MCS is an area of investigation, general indications for referral for MCS therapy include patient with LVEF<25% and NYHA class III-IV functional status despite guideline-directed medical therapy (GDMT) including cardiac resynchronization therapy (CRT), when indicated, with either high predicted 1- to 2-year mortality or dependence on continuous parenteral inotropic support.

*The Heart Failure Society of America (HFSA)*

The HFSA published guidelines in 2010 on surgical approaches to the treatment of heart failure. The guidelines are based on evidence and expert opinion. The following recommendations were made regarding ventricular assist devices:

- Bridge to transplantation: 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. (Strength of Evidence B - cohort and case-control studies)

- Bridge to recovery: 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. (Strength of Evidence C - expert opinion)
- Destination Therapy: 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. (Strength of Evidence B - cohort and case-control studies)

**Total Artificial Hearts**

Bridge to Transplantation

*Nonrandomized Studies*

In 2004, the CardioWest Total Artificial Heart (now called the SynCardia Total Artificial Heart) received FDA approval for use as a bridge to transplant. The approval was based on the results of a nonrandomized, prospective study of 81 patients.[72] Patients had failed inotropic therapy and 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 of the TAH as a bridge to transplant. For example, Copeland et al. reported on 101 patients treated with the SynCardia artificial heart as a bridge to transplant.[73] All patients either met established criteria for mechanically assisted circulatory support, or were failing medical therapy on multiple inotropic drugs. The mean support time was 87 days, with a range of 1-441 days. Survival to transplant was 68.3% (69/101). Of the 32 deaths prior to transplant, 13 were due to multiple organ failure, 6 were due to pulmonary failure, and 4 were due to neurologic injury. Survival after transplant at 1, 5, and 10 years, respectively, was 76.8%, 60.5%, and 41.2%.

Destination Therapy

In currently available studies, the AbioCor Implantable Replacement Heart has only been used as destination therapy for end-stage patients with congestive heart failure.

*Nonrandomized Studies*

Torregrossa et al reported on 47 patients who received a TAH at 10 worldwide centers and had the device implanted for more than one year.[74] 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 patients (72%) were successfully transplanted, 12 patients (24%) died while on device support, and one patient (2%) was still supported. Device failure occurred in five patients (10%). Major complications were common, including systemic infection in 25 patients (53%), driveline infections in 13 patients (27%), thromboembolic events in nine patients (19%) and hemorrhagic events in seven patients (14%). Two of the deaths occurred secondary to device failure

Dowling and colleagues reported on the first seven patients in the AbioCor clinical trial.[75] The 30-day survival rate was 71% compared with the predicted survival rate of 13% with only medical therapy. At 60 days, 43% were still alive and as of July 2006 two patients were still alive, 234 and 181 days postoperatively and remain hospitalized. Deaths were due to intraoperative bleeding at the time of implantation, cerebrovascular accidents, pulmonary embolism, and multiorgan failure. No reports of serious device malfunction have been reported for the seven patients. Frazier and colleagues reported information on four additional patients receiving the AbioCor.[76] Using the same inclusion criteria as in the above RCT the device supported three patients for greater than 100 days, whereas a fourth patient expired at 53 days. There were no device related problems reported.

Section Summary

There is little evidence on the use of TAH as a bridge to transplantation, or as destination therapy, compared with the use of LVADs. The type of evidence on bridge to transplant is similar to that for LVADs (i.e., case series reporting substantial survival rates in patients without other alternatives). Therefore, this evidence is sufficient to conclude that TAH improves outcomes for these patients similar to LVADs, and 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 for use as destination therapy in patients who have no other treatment options, the available data on their use is extremely limited. There is insufficient evidence on the use of TAH as destination therapy to support conclusions about the efficacy of TAH in this setting.

Clinical Practice Guidelines for Total Artificial Hearts

No clinical practice guidelines from U.S. professional associations were found for total artificial hearts.

**Summary**

Ventricular Assist Devices

The evidence from numerous uncontrolled trials is sufficient to conclude that implantable ventricular assist devices (VADs) as a bridge to transplantation or recovery, or as destination therapy, improve survival in select patients who have no other survival options and would not otherwise be expected to survive. Therefore, implantable VADs may be considered medically necessary when the policy criteria are met.

The evidence on percutaneous ventricular assist devices (pVADs) does not support that these devices improve health outcomes for any indication. Three randomized controlled trials (RCTs) that compared pVAD with intra-aortic balloon pump (IABP) for patients in cardiogenic shock failed to demonstrate a mortality benefit, and reported higher complications associated with pVAD use. A moderately large RCT of pVAD support versus usual care in patients undergoing high-risk percutaneous coronary intervention (PCI) procedures was terminated early due to futility. It was determined that the study would not meet the prespecified endpoint of a 10% absolute decrease in complications. The evidence for patients with cardiogenic shock refractory to IABP is limited to case series, which are considered unreliable due to methodological limitations such as lack of randomized treatment assignment and lack of an adequate comparison group. These case series have reported improved hemodynamic parameters following pVAD placement. However, these uncontrolled series cannot determine if pVAD improves mortality rates, and high rates of complications are reported with pVAD use. Therefore, because of the lack of demonstrated benefits in high-quality trials, in addition to the high complication rates reported, the use of pVADs for all indications is considered investigational.

Total Artificial Hearts

The evidence from uncontrolled trials is sufficient to conclude that the use of a total artificial heart (TAH) as a bridge to heart transplantation improves survival and quality of life in patients who are not candidates for implantable ventricular assist devices and would not be expected to survive with other medical or surgical interventions. Therefore, total artificial hearts may be considered medically necessary as a bridge to heart transplantation in select patients.

Current evidence is insufficient to permit conclusions related to the impact on survival, quality of life, and complication rates of total artificial hearts (TAHs) as destination therapy for patients who are not candidates for heart transplantation. Therefore, the use of TAHs as destination therapy is considered investigational.

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**CROSS REFERENCES**

Surgical Ventricular Restoration, Surgery, Policy No. 149

Heart Transplant, Transplant, Policy No. 02

Heart/Lung Transplant, Transplant, Policy No. 03

Extracorporeal Membrane Oxygenation (ECMO) for the Treatment of Cardiac and Respiratory Failure in Adults, Medical, Policy No. 152

| CODES | NUMBER | DESCRIPTION |
|---|---|---|
| Note: There is no specific code for reporting prolonged extracorporeal percutaneous transseptal ventricular assist device; the appropriate code for reporting this procedure is 33999. | | |
| CPT | 33975 | Insertion of ventricular assist device; extracorporeal, single ventricle |
| | 33976 | Insertion of ventricular assist device; extracorporeal, biventricular |
| | 33977 | Removal of ventricular assist device; extracorporeal, single ventricle |
| | 33978 | Removal of ventricular assist device; extracorporeal, biventricular |
| | 33979 | Insertion of ventricular assist device, implantable intracorporeal, single ventricle |
| | 33980 | Removal of ventricular assist device, implantable intracorporeal, single ventricular |
| | 33981 | Replacement of extracorporeal ventricular assist device, single or biventricular, pump(s), single or each pump |
| | 33982 | Replacement of ventricular assist device pump(s); implantable intracorporeal, single ventricle, without cardiopulmonary bypass |
| | 33983 | Replacement of ventricular assist device pump(s); implantable intracorporeal, single ventricle, with cardiopulmonary bypass |
| | 33990 | Insertion of ventricular assist device, percutaneous including radiological supervision and interpretation; arterial access only |
| | 33991 | Insertion of ventricular assist device, percutaneous including radiological supervision and interpretation; both arterial and venous access, with transseptal puncture |
| | 33992 | Removal of percutaneous ventricular assist device at separate and distinct session from insertion |
| | 33993 | Repositioning of percutaneous ventricular assist device with imaging guidance at separate and distinct session from insertion |
| | 0051T | Implantation of a total replacement heart system (artificial heart) with recipient cardiectomy |
| | 0052T | Replacement or repair of thoracic unit of a total replacement heart system (artificial heart) |

| CODES | NUMBER | DESCRIPTION |
|---|---|---|
| | 0053T | Replacement or repair of implantable component or components of total replacement heart system (artificial heart) excluding thoracic unit |
| HCPCS | Q0478 – Q0509 | Ventricular assist device accessories, code range |