



BlueCross BlueShield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association.

Total Artificial Hearts and Implantable Ventricular Assist Devices

Policy # 00246

Original Effective Date: 01/20/2010

Current Effective Date: 08/20/2014

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Post-cardiotomy Setting/Bridge to Recovery

Based on review of available data, the Company may consider implantable ventricular assist devices (VADs) with U.S. Food and Drug Administration (FDA) approval or clearance in the postcardiotomy setting in patients who are unable to be weaned off cardiopulmonary bypass to be **eligible for coverage**.

Bridge to Transplantation

Based on review of available data, the Company may consider implantable ventricular assist devices (VADs) with U.S. Food and Drug Administration (FDA) approval or clearance 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 to be **eligible for coverage**.

Based on review of available data, the Company may consider implantable ventricular assist devices (VADs) with U.S. Food and Drug Administration (FDA) approval or clearance, including humanitarian device exemptions, 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 to be **eligible for coverage**.

Based on review of available data, the Company may consider total artificial hearts (TAHs) with U.S. Food and Drug Administration (FDA)-approved devices as a bridge to heart transplantation for patients with biventricular failure who have no other reasonable medical or surgical treatment options, who are ineligible for other univentricular or biventricular support devices, 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 to be **eligible for coverage**.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*



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Destination Therapy

Based on review of available data, the Company may consider implantable ventricular assist devices (VADs) with U.S. Food and Drug Administration (FDA) approval or clearance may be considered **medically necessary** as destination therapy with end-stage heart failure patients who are ineligible for human heart transplant and who meet the following "REMATCH Study" criteria to be **eligible for coverage**.

Patient Selection Criteria

Coverage eligibility will be considered when the following criteria are met:

- New York Heart Association (NYHA) class IV heart failure for ≥ 60 days, or patients in NYHA class III/IV for 28 days, received ≥ 14 days' support with intra-aortic balloon pump (IABP) or dependent on IV inotropic agents, with two failed weaning attempts.

In addition, patients must not be candidates for human heart transplant for one or more of the following reasons:

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

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Other Indications

Based on review of available data, the Company considers other applications of implantable ventricular devices or total artificial hearts (TAHs) including, but not limited to, the use of total artificial hearts (TAHs) as destination therapy. The use of non-U.S. Food and Drug Administration (non-FDA) approved or cleared implantable ventricular assist devices (VADs) or total artificial hearts (TAHs) is considered to be **investigational**.*

Based on review of available data, the Company considers percutaneous ventricular assist devices (pVADs) for all indications to be **investigational**.*

Background/Overview

A VAD is a mechanical support attached to the native heart and vessels to augment cardiac output. The 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 who are not candidates for transplantation. The VAD has also been used as a bridge to recovery in patients with reversible conditions affecting cardiac output.

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.



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Heart transplantation improves quality of life and has survival rates at 1, 5, and 10 years of 88%, 74%, and 55%, respectively. The supply of donor organs has leveled off, while candidates for transplants are increasing, compelling the development of mechanical devices.

Initial research into mechanical assistance for the heart focused on the TAH, a biventricular device which 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.

VADs. Implantable VADs are attached to the native heart, which may have enough residual activity to withstand a device failure in the short term. In reversible conditions of heart failure, 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 use a pump, which provides continuous flow. Continuous devices may move blood in rotary or axial flow.

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 otherwise 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 cardiomy affecting the ventricular wall may preclude VAD use.

Percutaneous ventricular assist devices. Devices in which most 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, ie, are not implanted. These may be referred to as pVADs. The pVADs are placed through the femoral artery. Two different pVADs have been developed, the TandemHeart[™]† (Cardiac Assist[™], Pittsburgh, PA)‡, and the Impella[®] device (AbioMed[™], Aachen, Germany)‡. 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.



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

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

FDA or Other Governmental Regulatory Approval

U.S. FDA

Total Artificial Heart

In October 2004, device CardioWest™ Temporary Total Artificial Heart (SynCardia Systems Inc., Tucson, AZ) was approved by the U.S. FDA through the premarket approval process (PMA) for use as a bridge to transplant in cardiac transplant-eligible candidates at risk of imminent death from biventricular failure. Also, the temporary CardioWest Total Artificial Heart (TAH-t) is intended for use inside the hospital. In April 2010, FDA approved a name-change to SynCardia Temporary Total Artificial Heart.

In September 2006, device AbioCor® Implantable Replacement Heart System (AbioMed Inc., 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 ventricular assist device (LVAD) 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 is requiring the company to provide a comprehensive patient information package to patients and families. To further refine and improve the use of this artificial heart technology, AbioMed will conduct a postmarketing study of 25 additional patients. The postmarketing study was recommended by the Circulatory Systems Devices Panel, a part of FDA's Medical Devices Advisory Committee.

Ventricular Assist Devices

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

- (1) Candidate for cardiac transplantation,
- (2) Imminent risk of dying before donor heart procurement, and
- (3) 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 who are 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 in the company of a trained caregiver. In November 2003, supplemental approval was given to market the device



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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 delete Paracorporeal VAD use.

In February 2004, FDA approved the DeBakey VAD^{®†} Child under the HDE approval process. According to FDA, this device is indicated under HDE 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 (Thoratec, Pleasanton, CA) was approved by FDA through the PMA 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 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 NYHA 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 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 via HDE. The indications for this device are 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 Inc., Miami Lakes, FL) through PMA. The device is approved as a bridge to cardiac transplantation in patients at risk for death from refractory end stage left ventricular heart failure.

Percutaneous Ventricular Assist Devices (circulatory assist devices)

The Impella Recover LP 2.5 Percutaneous Cardiac Support System (Abiomed, Aachen, Germany) received FDA 510(k) approval in May 2008 for short-term (<6 hours) use in patients requiring circulatory support. The TandemHeart (Cardiac Assist, Pittsburgh) received a similar 510(k) approval for short-term circulatory support in September 2005.



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Device	Manufacturer	Date of Initial Approval	Method of FDA Clearance	Indication
VAD				
Thoratec IVAD	Thoratec	Aug 2004	PMA Supplement	Bridge to transplant and postcardiotomy
DeBakey VAD Child	MicroMed	Apr 2004	HDE	Bridge to transplant in children 5-16 y of age
HeartMate II	Thoratec	Apr 2008	PMA	Bridge to transplant and destination
Centrimag	Levitronix	Oct 2008	HDE	Postcardiotomy
Berlin Heart EXCOR Pediatric VAD	Berlin	Dec 2011	HDE	Bridge to transplant
HeartWare Ventricular Assist	HeartWare	Dec 2012	PMA	Bridge to transplant

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System

pVAD

Impella	Abiomed	May 2008	510(k)	Partial circulatory support using an extracorporeal bypass control unit for periods up to 6 h
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TandemHeart	Cardiac Assist	Sep 2005	510(k)	Temporary left ventricular bypass of ≤6 h
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Several other devices are in clinical trials or awaiting FDA review.

Centers for Medicare and Medicaid Services (CMS)

Medicare has a national coverage determination for artificial hearts and related devices, including VADS.

The national coverage policy mandates coverage for VADs in the *post-cardiotomy setting* as long as the following conditions are met:

- The VAD has approval from FDA for post-cardiotomy support.
- The VAD is used according to the FDA-approved labeling instructions.

The 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 and listed as a candidate 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 national coverage policy 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.

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- Patient selection: VADs are covered for patients who have chronic end-stage heart failure (New York Heart Association class IV end-stage left ventricular failure) who are not candidates for heart transplantation, and meet all of the following conditions:
 - Have failed to respond to optimal medical management (including beta-blockers and ACE inhibitors if tolerated) for at least 45 of the last 60 days, or have been balloon pump-dependent for 7 days, or IV inotrope-dependent for 14 days; and,
 - Have a left ventricular ejection fraction (LVEF) <25%, and,
 - Have demonstrated functional limitation with a peak oxygen consumption of ≤ 14 mL/kg/min unless balloon pump- or inotrope-dependent or physically unable to perform the test.
- Facility criteria: As of an October 30, 2013, decision memo on a National Coverage Analysis for VADs, the CMS concluded that the evidence is sufficient to conclude that VADs implanted in facilities that meet certain criteria improve health outcomes. Facilities currently credentialed by the Joint Commission for placement of VADs as DT [destination therapy] may continue as Medicare-approved facilities until October 30, 2014. At the conclusion of this transition period, these facilities must be in compliance with the following criteria as determined by a credentialing organization. As of the effective date, new facilities must meet the following criteria as a condition of coverage of this procedure:
 - 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 embodies collaboration and dedication across medical specialties to offer optimal patient-centered care. Collectively, the team must ensure that patients and caregivers have the knowledge and support necessary to participate in shared decision making and to provide appropriate informed consent. 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. The team must include, at a minimum, all of the following:
 - At least one physician with cardiothoracic surgery privileges and individual experience implanting at least 10 durable, intracorporeal, left ventricular VADs as BTT [bridge to transplant] or DT over the course of the previous 36 months with activity in the last year.
 - At least one cardiologist trained in advanced heart failure with clinical competence in medical and device-based management including VADs, and clinical competence in the management of patients before and after heart transplant.
 - A VAD program coordinator.
 - A social worker.
 - A palliative care specialist.
 - Facilities must be credentialed by an organization approved by CMS.

The national coverage policy 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 and addresses one of the following questions:

- Were there unique circumstances such as expertise available in a particular facility or an unusual combination of conditions in particular patients that affected their outcomes?
- What will be the average time to device failure when the device is made available to larger numbers of patients?



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- Do results adequately give a reasonable indication of the full range of outcomes (both positive and negative) that might be expected from more widespread use?

Clinical trials that meet the above requirements will be listed on the CMS website (http://www.cms.gov/MedicareApprovedFacilities/06_artificialhearts.asp).

Rationale/Source

The most recent literature review was performed for the period from July 2012 through January 9, 2014. The literature review focuses on 3 types of devices: (1) LVADs, (2) TAHs, and (3) pVADs. The literature review addresses short-term use of the devices as a bridge to recovery or transplantation. The LVADs and TAHs are also evaluated as longer-term destination therapy for patients who are not transplant candidates. Following is a summary of the key literature to date.

LVADs

LVADs as Bridge to Recovery

Five studies of the Centrimag Right Ventricular Assist Device (RVADs) included between 12 and 32 patients, most of whom received biventricular devices. Indications (and numbers of patients) in these 5 studies were: support for postcardiotomy cardiogenic shock (bridge to recovery, n=53), bridge to long-term device implantation (n=9), treatment of right heart failure in patients who previously received LVADs (n=15), bridge to later decision when neurologic status is clarified (n=16), and acute donor graft failure (n=6). 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.

LVADs may have a role in bridging patients to recovery, particularly if there is reverse remodeling of the left ventricle. A number of relatively small, noncomparative studies have evaluated LVADs as bridge-to-recovery therapy. 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. Eleven of 15 patients had enough myocardial recovery to undergo LVAD explantation; 2 patients 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. 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 ACE inhibitors, beta blockers, and adosterol antagonists followed by the β_2 -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 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 evaluated 67 patients with heart failure who had undergone LVAD implantation for severe heart failure. 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-



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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.

Section Summary

The studies previously outlined indicate that a subset of patients who receive an LVAD as a bridge to transplant or as destination therapy demonstrate improvements in their cardiac function, sometimes to the point that they no longer require the LVAD. However, questions remain about defining and identifying the population most likely to experience cardiac recovery with LVAD placement. One clearly defined population in which the potential for myocardial recovery exists is in the postcardiotomy setting. The current evidence is insufficient to allow the identification of other heart failure patient populations who might benefit from the use of an LVAD as a specific bridge-to-recovery treatment strategy. Ongoing research studies are addressing this question, along with protocols for transitioning patients off LVAD use.

LVADs as Bridge to Transplant

A 1996 TEC Assessment concluded that LVADs can provide an effective bridge to transplantation. Goldstein et al published a more recent review. It should be recognized that LVADs do not change the number of patients undergoing heart transplantation due to the fixed number of donor hearts. However, the VAD will categorize its recipient as a high-priority heart transplant candidate.

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 posttransplant survival, thus improving the use of donor hearts. Currently available implantable LVADs consist of pulsatile devices that require stiff power vent lines that perforate the skin and implantable pump chambers, as well as nonpulsatile axial flow systems of smaller size and lower noise levels.

In 5 reports published from 2007 to 2008, with samples ranging from 32 to 279 patients, most participants received the continuous-flow device as a bridge to transplantation. Survival rates at 6 months were between 67% and 87%, and between 50% and 80% at 1 year. These rates are similar to those reported from a federal circulatory support device registry, the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS). An additional report from INTERMACS comparing the HeartMate II with other LVAD devices for patients who received them with a bridge to transplantation indication 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 compared HeartMate I and HeartMate II recipients at a single center, finding the same 1-year survival and similar rates of subsequent development of right heart failure. Serious adverse events occurring after HeartMate II implantation include bleeding episodes requiring reoperation, stroke, infection, and device failure.

A systematic review published in 2011 examined the evidence on the effect of LVADs on posttransplant outcomes. This review included 31 observational studies that compared outcomes of transplant in patients who did and did not have pretransplant LVAD. Survival at 1 year was more likely in patients who had LVAD treatment, but this benefit was confined 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 was not different from patients who were not treated with an LVAD (RR=1.08; 95% CI,



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0.95 to 1.22). There was no difference in the risk of rejection between patients who did and did not receive LVAD treatment.

Additional studies published since the systematic review continue to report high success rates in bridging to transplant. In 2011, Strueber et al published a case series of 50 patients awaiting heart transplantation treated with HeartWare VAD. Patients were followed until transplantation, myocardial recovery, device explant, or death. The median duration of time on the LVAD was 322 days. Nine patients died; 3 from sepsis, 3 from multiple organ failure, and 3 from hemorrhagic stroke. At the end of follow-up, 20 patients had undergone transplant (40%), 4 had the pump explanted (8%), and the remaining 17 continued on pump support (34%). The most common complications were infection and bleeding. A total of 21 patients had infections (42%), and 5 patients had sepsis (10%). Bleeding complications occurred in 15 patients (30%), 10 of whom (20%) required surgery for bleeding.

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. The study enrolled 140 patients who were 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 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.

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 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.

Pediatric patients. There is 1 FDA-approved device, the EXCOR Pediatric VAD, via the HDE process, available for use as a bridge to cardiac transplant in children. This HDE 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. Using the United Network for Organ Sharing (UNOS) database, Davies et al reported on use of VADs in pediatric patients undergoing heart transplantation. Their analysis concluded that pediatric patients requiring a pretransplantation VAD have similar long-term survival to those not receiving mechanical circulatory support.

Following FDA approval, Fraser et al 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



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heart transplant. Patients were divided into 2 groups based on body surface area; a historic control group of children receiving circulatory support with extracorporeal membrane oxygenation (ECMO) from the Extracorporeal Life Support Organization registry, matched in a 2:1 fashion with study participants based on propensity-score matching. For participants in cohort 1 (body surface area, $<0.7 \text{ m}^2$), 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 (body surface area, 0.7 to $<1.5 \text{ m}^2$), 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 (in 42% and 50% of cohort 1 and cohort 2, respectively), infection (in 63% and 50% of cohort 1 and cohort 2, respectively), and stroke (in 29% of both cohorts).

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. This study included a broader patient population than the Fraser et al study. 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.

Section Summary

In adults, the evidence on the efficacy of LVADs as bridge to transplant consists of numerous uncontrolled trials and trials comparing different LVAD devices of patients who have no other treatment options. In children, the evidence consists of several uncontrolled trials and 1 trial with historical controls. These studies report that substantial numbers of patients survive to transplant in situations in which survival would not be otherwise expected. Despite the lack of high-quality controlled trials, this evidence is sufficient to determine that outcomes are improved in patients who have no other options for survival. The impact of pretransplant LVADs on survival from transplant is uncertain, with some studies reporting worse survival in patients receiving LVADs, but other studies reporting similar or improved survival.

LVADs as Destination Therapy

The policy regarding LVADs as destination therapy is based on 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 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 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; NYHA class was significantly improved, as was quality of life among those living to 12 months.



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- 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 et al published an extended 2-year follow-up of patients in the REMATCH trial, which found that survival and quality-of-life benefits were still apparent. In addition, this study and other case series suggest 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 is a concern; for example, at one participating institution, all 6 long-term survivors required device change-outs. Next generation devices consisting of smaller continuous flow devices are eagerly anticipated.

After publication of the REMATCH study results, Rogers et al published results from a prospective, nonrandomized clinical 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 NYHA functional class IV symptoms and who failed weaning from inotropic support were offered a Novacor LVAD; 18 of these 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.

Section Summary

The main piece of evidence on the efficacy of LVADs as destination therapy in patients who are not transplant candidates is from a multicenter randomized controlled trial (RCT), the REMATCH study. This trial reported that the use of LVADs led to improvements in survival, quality of life, and functional status. This evidence is sufficient to establish that health outcomes are improved for this patient population.

Comparative Efficacy of Continuous Flow versus Pulsatile Flow Devices

In December 2009, Slaughter et al published data from an unblinded randomized multicenter trial comparing a continuous flow device with a pulsatile device. Subjects were randomly assigned 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, free of disabling stroke or need for device replacement. Continuous-flow patients ($n=134$) reached the primary outcome at a rate of 46% (95% CI, 38 to 55) compared with pulsatile-flow patients' ($n=66$) rate of 11% (95% CI, 3 to 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 end point; 2-year death rate also favored this device (58% vs 24%, respectively; $p=0.008$). Stroke and death (within 2 years of implantation) were similar in the 2 groups (stroke rate, 12%; death rate, 36%). Quality-of-life scores were also similar in the 2 groups. Although unblinded, this randomized trial adds to the evidence favoring continuous-flow devices.

Nativi et al published a nonrandomized comparison of pulsatile versus continuous flow devices using data from the registry of the International Society for Heart and Lung Transplantation on 8557 patients undergoing transplant. 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



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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 with the second time period (RR=1.30; 95% CI, 1.03 to 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 with the pulsatile group (RR=1.25; 95% CI, 1.03 to 1.65; p=0.03).

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 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 1 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 1 database study with large numbers of patients, have not reported important differences between devices on clinical outcomes.

TAH

TAH as Bridge to Transplant

The FDA approval of the CardioWest TAH was based on the results of a nonrandomized, prospective study of 81 patients. 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 with 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. 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 to 441 days. 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. Survival after transplant at 1, 5, and 10 years, respectively, was 76.8%, 60.5%, and 41.2%.

TAH as Destination Therapy

Data concerning the artificial heart are available from information concerning the FDA approval and from a published article describing results for the first 7 patients. FDA indicated that their decision was based on the company's laboratory and animal testing and on a small clinical study of 14 patients that was conducted by Abiomed. The patients had a 1-month survival prognosis of not more than 30%, were not eligible for cardiac transplants, and were felt to not benefit from VAD therapy. The study was reported to show that the device is safe and has likely benefit for people with severe heart failure whose death is imminent and for



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whom no alternative treatments are available. Of the 14 patients in the study, 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. Device-related infection was "non-existent."

This device shows technologic progress, and these initial results are encouraging; however, a number of questions remain. These questions may be answered once the results of the 14-patient study are published, or data on a larger group of patients may be needed. One issue is to further analyze relevant patient outcomes (eg, complications, quality of life, survival). Therefore, based on current information, this device is considered investigational.

Section Summary

There is a smaller amount of 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, ie, 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. There is insufficient evidence on the use of TAH as destination therapy to support conclusions.

pVADs

pVADs as an Alternative to Intra-Aortic Balloon Pump in Cardiogenic Shock

Three RCTs have been published that compare pVADs with IABPs for patients with cardiogenic shock, along with a systematic review and meta-analysis of these 3 trials. The meta-analysis was published in 2009 by Cheng et al. The 3 RCTs enrolled a total of 100 patients, 53 treated with a pVAD and 47 treated with an IABP. All 3 study populations included patients with acute MI and cardiovascular shock; 1 of the trials restricted this population to patients who were postrevascularization in the acute MI setting. The primary outcomes reported were 30-day mortality, hemodynamic measures of left ventricular (LV) pump function, and adverse events.

None of the 3 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 to 1.66; $p=0.80$). All 3 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 12.8 mm Hg (95% CI, 3.6 to 22.0; $p<0.001$), and a decrease in pulmonary capillary wedge pressure of 5.3 mm Hg (95% CI, 1.2 to 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 to 3.93). Leg ischemia was also more common in the pVAD group, but this difference did not meet statistical significance (RR=2.59; 95% CI, 0.75 to 8.97; $p=0.13$).



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Case series of patients treated with pVADs as an alternative to IABP in cardiogenic shock have been published, and report high success rates as a bridge to alternative therapies. However, these studies do not add much to the evidence on efficacy that is reported from the RCTs.

pVADS as Bridge to Recovery in 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 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, cardiac index increased from 0.52 ± 0.8 L/min/m² to 3.0 ± 0.9 L/min/m² ($p < 0.001$), and the systolic blood pressure increased from 75 ± 15 mm Hg to 100 ± 15 mm 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 4 patients (3.4%); femoral artery dissection or perforation in 2 patients (1.7%); stroke in 8 patients (6.8%); coagulopathy in 13 patients (11.0%).

pVADs Ancillary Support in High-Risk Patients Undergoing Invasive Cardiovascular Procedures

The PROTECT trial intended to evaluate whether the Impella 2.5 system improved outcomes for patients undergoing high-risk percutaneous coronary intervention (PCI) procedures. 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 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 2 patient deaths within 30 days (10%), and 2 patients had a periprocedural MI (10%). An additional 2 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 patients enrolled revealed that the primary end point could not be reached. At the point that the data safety and monitoring board stopped the study, 452 patients had been enrolled, 3 of whom withdrew consent and 1 who died. Results were published by O'Neill et al in 2012. 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 end point 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.

A few other case series have described pVAD use in high-risk patients undergoing an invasive cardiac procedure. Sjauw et al performed a retrospective analysis of 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



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patients. There was 1 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 stroke (0.7%) and no MIs were reported. Maini et al performed a similar retrospective analysis of 175 patients undergoing high-risk PCI with pVAD support with 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%), ventricular tachycardia, or cardiopulmonary resuscitation (2.8%); other vascular complications such as 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%).

Section Summary

pVADs have been tested in RCTs and uncontrolled studies of patients with cardiogenic shock and in patients undergoing high-risk cardiac interventions. The RCTs do not report a benefit for use of pVADs. In addition, both the RCTs and case series report high rates of adverse events that may outweigh any potential benefits. As a result, the evidence on pVADs does not support an improvement in health outcomes for patients with cardiogenic shock or in patients undergoing high-risk cardiac interventions.

Ongoing trials (all devices)

A search of the website ClinicalTrials.gov identified the following ongoing trials that will include outcomes associated with mechanical circulatory support devices:

- **The Remission From Stage D Heart Failure (RESTAGE-HF)** trial (NCT01774656). This is a noncomparative interventional study to determine the proportion of subjects who have enough improvement in ventricular function after undergoing a standardized LVAD plus pharmacologic recovery treatment and testing protocol to allow removal of the LVAD. Eligible subjects will have NYHA class IIIB/IV heart failure and be eligible for the HeartMate II implant as bridge to therapy or destination therapy. The HeartMate II device will be combined with a standardized protocol of medical therapy to enhance cardiac remodeling, including carvedilol, spironolactone, losartan, and digoxin. Enrollment is planned for 40 patients. The estimated study completion date is December 2017.
- **A Clinical Trial to Evaluate the HeartWare Ventricular Assist System (ENDURANCE SUPPLEMENTAL TRIAL)** (NCT01966458). This is a prospective, randomized, unblinded controlled trial to assess the incidence of stroke in patients with advanced heart failure receiving the HeartWare ventricular assist system who received optimal blood pressure management and to compare stroke-free success among those receiving the HeartWare device to those receiving other FDA-approved LVADs for destination therapy. Patients will be randomized to either an experimental group and receive the HeartWare device, or an active comparator group. Enrollment is planned for 429. The estimated study completion date is October 2016.
- **A Prospective Study to Evaluate the Safety and Efficacy of the EVAHEART LVAS for Use as a Bridge-to-Transplant (NCT01187368)**. This is a prospective, noncomparative study to evaluate



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the safety and efficacy of the EVAHEART left ventricular assist system in patients with end-stage heart failure who are candidates for heart transplant. Enrollment is planned for 20 patients. The estimated study completion date is July 2016.

- **Evaluation of the Jarvik 2000 Left Ventricular Assist System With Post-Auricular Connector--Destination Therapy Study (NCT01627821).** This is a prospective, randomized, unblinded controlled trial to compare the Jarvik 2000 Left Ventricular Assist system with Post-Auricular Connector to an active control group treated with the Thoratec HeartMate II for destination therapy in patients with late-stage heart failure who are ineligible for heart transplant. Enrollment is planned for 350 patients. The estimated study completion date is December 2016.

Clinical Input Received Through Physician Specialty Societies and Academic Medical Centers

In response to requests, input was received through 2 physician specialty societies and 5 academic medical centers while this policy was under review in May 2014. 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.

Vetting focused on the use of percutaneous ventricular assist devices in accordance with the American Heart Association/American College of Cardiology guidelines (2013) and the use of TAH as destination therapy. All of those providing input supported the use of implantable ventricular assist devices as destination therapy subject to the guidelines in the policy statements. Most of those providing input considered TAHs to be investigational for destination therapy; reviewers noted that there is limited clinical trial data to support the use of TAHs as destination therapy.

Most of those providing input considered pVADs to be investigational as a “bridge to recovery” or “bridge to decision” and for all other indications. Some reviewers 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.

Summary

A VAD is a mechanical support attached to the native heart and vessels to augment cardiac output. The TAH replaces the native ventricles and is attached to the pulmonary artery and aorta; the native heart is typically removed. 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 quality of life. A well-designed clinical trial, with 2 years of follow-up data, demonstrates an advantage of implantable VADs as destination therapy for patients who are ineligible for heart transplant. Despite an increase in adverse events, both mortality and quality of life appear to be improved for these patients. Therefore, LVADs may be considered medically necessary as a bridge to transplant and as destination therapy in patients who are not transplant candidates.



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The evidence for TAH in these settings is less robust. However, given the limited evidence from case series and the lack of medical or surgical options for these patients, 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 an LVAD. TAH may be considered medically necessary for this purpose. There is insufficient evidence on the use of TAH as destination therapy, and TAH is considered investigational for this purpose.

The evidence on pVADs does not support that these devices improve health outcomes. Three RCTs of pVAD versus IABP for patients in cardiogenic shock failed to demonstrate a mortality benefit and reported higher complications associated with pVAD use. A fourth RCT 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. Case series of patients with cardiogenic shock refractory to IABP have reported improved hemodynamic parameters following pVAD placement. However, these uncontrolled series cannot determine if pVAD improves mortality, and high rates of complications are reported with pVAD use. Because of the lack of demonstrated benefits in clinical trials, and the high complication rates reported, the use of pVAD for all indications is considered investigational.

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Coding

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Total Artificial Hearts and Implantable Ventricular Assist Devices

Policy # 00246

Original Effective Date: 01/20/2010

Current Effective Date: 08/20/2014

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Code Type	Code
CPT	0051T, 0052T, 0053T, 33975, 33976, 33977, 33978, 33979, 33980, 33981, 33982, 33983, 33990, 33991, 33992, 33993, 93750
HCPCS	Q0478, Q0479, Q0480, Q0481, Q0482, Q0483, Q0484, Q0485, Q0486, Q0487, Q0488, Q0489, Q0490, Q0491, Q0492, Q0493, Q0494, Q0495, Q0496, Q0497, Q0498, Q0499, Q0500, Q0501, Q0502, Q0503, Q0504, Q0506, Q0507, Q0508, Q0509
ICD-9 Diagnosis	398.91, 402.01, 402.11, 404.01, 404.03, 404.11, 428.0
ICD-9 Procedure	37.52, 37.53, 37.54, 37.62, 37.63, 37.65, 37.66, 37.68

Policy History

Original Effective Date: 01/20/2010

Current Effective Date: 08/20/2014

01/07/2010 Medical Policy Committee approval

01/20/2010 Medical Policy Implementation Committee approval. New policy.

01/06/2011 Medical Policy Committee approval

01/19/2011 Medical Policy Implementation Committee approval. Title changed. Policy statements revised to address only implantable VADs and total artificial hearts.

04/12/2012 Medical Policy Committee approval

04/25/2012 Medical Policy Implementation Committee approval. Percutaneous VADs added to policy investigational statement and rationale.

04/04/2013 Medical Policy Committee review

04/24/2013 Medical Policy Implementation Committee approval. Added "Implantable" to the beginning of the 2nd coverage statement under Bridge to Transplant to make it consistent with the other coverage statements and the focus of the policy. Coverage statement on children amended; age range changed from 5-16 to 0-16, reflecting the approval of the BERLIN heart EXCOR device for pediatric patients aged 0-16. Clause added to coverage statement on total artificial hearts that says "...or are undergoing evaluation to determine candidacy for heart transplantation...".

08/07/2014 Medical Policy Committee review

08/20/2014 Medical Policy Implementation Committee approval. Coverage statement unchanged.

Next Scheduled Review Date: 08/2015

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Total Artificial Hearts and Implantable Ventricular Assist Devices

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***Investigational** – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
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 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
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- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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