

## REVIEW ARTICLE

# Ventricular assist device for advanced heart failure

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### ABSTRACT

Heart failure (HF) continues to be a highly prevalent disease, affecting 1–2% of the population in developed countries, therefore constitutes a health problem due to its high cost. Despite the progress made in drug treatment and implantation devices, the prognosis is poor. About 5% of patients diagnosed with heart failure are in advanced stage or stage D. Heart transplantation (HT) has become the preferred treatment for this high-risk group in the past 30 years. Unfortunately, in addition to the limitation of the current shortage of donors, there is only a limited number of patients meet the appropriate age and with the absence of comorbidities necessary to access this treatment. Due to this and the long waiting lists worldwide, the development and use of ventricular assist devices (VAD) are increasing. In view of the quality of life of patients with this serious disease, these devices improve the short-term and long-term survival rate and gradually reduce the complication rate. These benefits not only provide a choice for patients waiting for HT, but also give those with reversible contraindications the time and opportunity to become suitable candidates or, if impossible, eventually use it as a target treatment. However, these devices have many limitations: their cost, durability, incidence of complications and their limited application. Technological advances in mitigating complications, increased experience in management centers and their promotion to reduce costs are strategies that will continue to strengthen the use of VAD in patients with advanced heart failure.

**Keywords:** ventricular assist device; heart failure; heart transplantation; mechanical circulatory support; complications

## 1. Introduction

Heart failure (HF) is still a disease with high incidence, affecting 1–2% of the population in developed countries, so it is a health problem because of its high cost<sup>[1]</sup>. Despite the progress made in drug treatment and implantation devices, the prognosis is poor. About 5% of patients diagnosed with heart failure are in the late stage or stage D<sup>[2]</sup>.

Advanced HF is currently defined as<sup>[3]</sup>:

Presence of symptoms at rest or with minimal exertion, function class (FC) grade III-IV according to the New York Heart Association (NYHA). Clinical evidence compatible with systemic hyperemia and/or hypoperfusion. Severe cardiac insufficiency: Left ventricular ejection fraction (LVEF) <30%. Doppler echocardiogram with pseudonormal or restrictive pattern in the mitral flowgram. Left filling pressure increased: Pulmonary artery occlusion

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pressure >16 mm Hg and/or right atrial pressure (RA) >12 mm Hg. Increase natriuretic peptide in the absence of noncardiac causes. Severe functional damage: Exercise intolerance. 6-minute walk test <300 meters. Peak oxygen consumption <12–14 ml/kg/min. Hospitalization history of decompensated heart failure in the past 6 months. Despite the best drug therapy and cardiac resynchronization therapy, all previous criteria exist.

In the past three decades, heart transplantation has become the preferred treatment for this high-risk group. Unfortunately, a small percentage of patients meet the appropriate age and with the absence of

comorbidities necessary to access this treatment, in addition to the current shortage of donors. About 2,200 HT scan performed per year in the United States and 250–300 HT per year in Spain<sup>[4,5]</sup>. For a long time, HT list has been the basis for the development of various mechanical circulatory support devices (MCS).

In recent years, both short-term and long-term ventricular assist devices (VADs) have developed greatly; currently, its indication is well defined as abridging therapy to recovery, bridge to HT, bridge to decision, bridge to candidacy or destination therapy (**Table 1**).

**Table 1.** Indications for mechanical circulatory support

Bridge to decision/bridge to bridge	Short-term MCS is used in patients with cardiogenic shock to stabilize hemodynamic parameters and target organ perfusion to evaluate other treatments, such as long-term MCS or HT.
Bridge to candidacy	Use MCS to improve perfusion, reverse pulmonary hypertension, or provide cancer-free time to make HT qualified.
Bridge to Transplant	Due to the high mortality of patients before HT, left ventricular or biventricular assist is used to maintain the survival of patients.
Bridge to recovery	Left ventricular or biventricular assist is used to maintain patient survival until ventricular function is restored.
Destination therapy	Long-term MCS in end-stage HF ineligible for HT.

MCS: Mechanical circulatory support. HT: Heart transplant. HF: Heart failure.

## 2. History

In 1953, the modern era of cardiac surgery began. Cardiopulmonary bypass was first used for the rehabilitation of patients with cardiogenic shock after cardiac surgery, which laid a foundation for the further development of VADs<sup>[6]</sup>. By the 1960s, simple VADs began to replace cardiopulmonary bypass to treat this very serious heart disease. The use of implantable artificial ventricles, including a pneumatic device, was first reported in 1963<sup>[7]</sup> to connect the left atrium (LA) to the descending aorta to provide 4-day partial ventricular support during post-operative cardiac surgery. In 1966, DeBakey successfully used the first pneumatic VADs for 10 days in postoperative heart surgery<sup>[8]</sup>. In 1969, it was reported that the whole artificial heart was used as a bridge to connect HT<sup>[9]</sup>. After these events, people have been looking for simple and lasting implant devices for decades. In the 1970s, the first generation

of extracorporeal pneumatic VAD appeared, which could remain in place for a few days due to the high rates of hemolysis and thrombosis, with high costs and low effectiveness as pump. In 1984, Novacor successfully implanted its electric pulse device into the left ventricle as a bridge for transplantation<sup>[10]</sup>. In 1985, Jarvik 7 artificial heart successfully realized the first HT bridge. Since then, the so-called assists era of first generation, all with pulsatile flow, but only three subtypes have been approved by the U.S. Food and Drug Administration (FDA) as a bridge to transplantation:

(1) Left intracorporeal support type, being the first to demonstrate its effectiveness was Thoratec IP LVAS in 1995, a pneumatic device; subsequently, the HeartMate VE/XVE with electric pulsating plate was launched.

(2) Univentricular or biventricular support paracorporeal devices, neumatic such as the

Thoratec PVAD.

(3) Devices of artificial heart type, such as Cardiowest, currently known as Syncardia. After the publication of REMATCH, pulse technology showed its advantages over medical treatment. After 12-month follow-up, the mortality was reduced by 48% at the expense of high rate of complications of VADs<sup>[11]</sup>.

The focus of the second-generation device is on smaller size, lower complication rate and higher durability, so that it can be used as the destination therapy or bridge to transplantation. Continuous and axial flow pumps have emerged, such as Jarvik 2,000, Heart Assist 5 or Incor from Berlin Heart. The HeartMate II was approved as a bridge to transplantation in 2008 and as a destination therapy in 2010 with obvious advantages compared with other pulse devices<sup>[12,13]</sup>. In recent years, the third-generation ventricular assist device has developed, continuous type devices, but of the centrifugal type. Among different devices, the HeartWare intrapericardial plant is the most prominent, and was approved by FDA in 2012 as a bridge to transplantation.

The latest device designed was the HeartMate III with pulsatility.

About short-term MCS, its development focuses on fast and simple implants, because in acute situations, stabilization is needed as a bridge to decision, recovery, implantation of a long-term device or HT. They have a more limited role and less evidence as a bridge to transplant indication. Some of the most used are Abiomed AV and BVS 5,000 pulsatile and extracorporeal type, but the support time is less than 10 days. Others, such as Thoratec PVAD or Excor Berlin Heart, were born as long-term devices and are currently classified as short-medium devices. The latest development in this field is CentriMag, which allows univentricular or biventricular support in possible combined with ECMO (ExtraCorporeal Membrane Oxygenation: Extracorporeal membrane oxygenation).

### 3. Type of ventricular assist device

The purpose of different VADs is to restore tissue perfusion and increase blood supply; however, their management may be a challenge, as well as the recognition of various complications that may occur with its use, some of which pose a threat to life. Therefore, according to different indications, treatment doctors must be familiar with different types of equipment, understand its mechanism, related physiology and the identification and treatment of complications.

Depending on its indication, VADs can be implanted as a paracorporeal or extracorporeal device (located outside the patient's body) or intracorporeally. The latter can be located in the pericardial space or under the diaphragm, or it can be a percutaneous type; regardless of the shape or location of the implant, all currently available systems have external controllers and power supplies<sup>[14]</sup>.

They can be classified according to the support they provide: left ventricular (LV), right ventricular (RV), or biventricular support. For patients with little residual cardiac function and low recovery opportunities, complete artificial heart may be an option to completely replace the function of natural heart.

The most common way to classify VAD is based on their usage time<sup>[15]</sup>:

Short term: hemodynamic support for days or weeks.

Percutaneous: Intra-aortic balloon counterpulsation, IMPELLA®, TANDEM-HEART®.

Surgery: ECMO-VA, CentriMag.

Long term: hemodynamic support, which can be extended for months to years.

INCORE, EXCOR, HeartMate I, HeartMate II, HeartWare, HeartMate III.

#### 3.1. Short time left ventricular assist device

Over the past few decades, these devices have

gained a place in supporting patients with cardiogenic shock refractory to medical treatment; as well as during high-risk surgery, such as percutaneous revascularization or arrhythmia ablation.

When ventricular support methods are properly selected and applied, it can effectively help as a bridge to recovery, bridge to bridge or HT. These devices can assist the left or right ventricle and, in some cases, provide biventricular assistance. Although their most common indication is not advanced HF, they can be safely used in acute events of this group of patients, in their stabilization and used until the decision of a more lasting therapy (bridging to decision or destination treatment) or they can serve to optimize the patient prior to implantation of a long-term equipment or performing HT (bridge to bridge or bridge to HT).

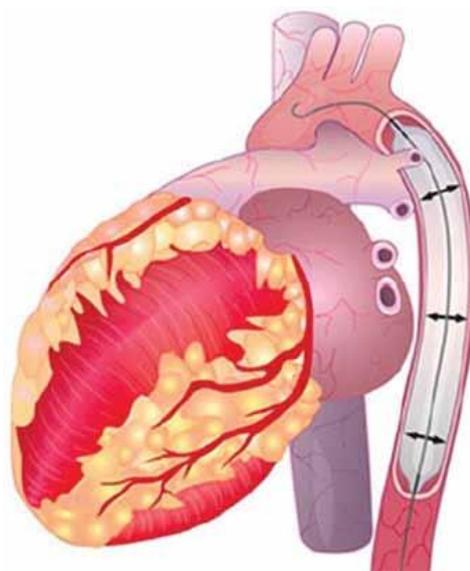
### ***Intra-aortic balloon counterpulsation***

Although its effectiveness in cardiogenic shock is controversial<sup>[16]</sup>, whether as a bridge of recovery or to HT, it is still a widely used treatment because of its higher availability compared with other MCS devices. Its implants are less complex, less invasive and have a low risk of complications. It can improve cardiac function by reducing afterload and improving myocardial oxygen demand. Its main disadvantage is its inability to partially or completely replace cardiopulmonary function.

It consists of a cylindrical balloon located in the descending aorta near the left subclavian artery and connected to the external pump and console through a flexible catheter (**Figure 1**). The concept of diastolic counterpulsation includes balloon inflation during relaxation, balloon deflation in early contraction during isovolumic contraction<sup>[17]</sup>, increasing coronary flow, decreasing left ventricular afterload, reducing myocardial oxygen consumption, increasing cardiac output and reducing parietal stress.

Its hemodynamic effect depends on: the volume of the balloon, the parameters programmed on the console, the position in the aorta, the relationship between the balloon size and the aorta, heart rhythm and heart rate, so its hemodynamic effect

can be variable. However, there is sufficient evidence that in patients with cardiogenic shock, systolic blood pressure decreased by 20%, diastolic blood pressure increased by 30%, average pulmonary artery pressure decreased by 23%, and cardiac output increased by 20–24%. Improving tissue perfusion and reducing myocardial oxygen consumption is one of its most important roles<sup>[18]</sup>. Complications were rare (0.5%), including lower extremity and renal ischemia. The mortality associated with the device is less than 0.05%.



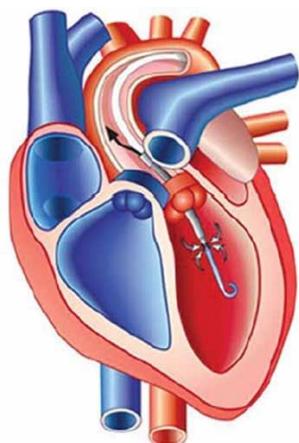
**Figure 1.** Schematic diagram of intra-aortic counterpulsation balloon.

### ***Impella system (ABIOMED Inc.)***

This is an axial flow system on a catheter that positioned through the aortic valve (**Figure 2**). The inflow port is located inside the left ventricle and the outflow port is in the aorta. In this way, it reduces ventricular pressure by providing non-pulsatile flow to the ascending aorta. There are several types of thrusters: 2.5 (2.5 L/minute of flow), CP (3.5 L/minute of flow), 5.0 (5 L/minute of flow), all of which can be used for percutaneous femoral implantation<sup>[19]</sup>. Contraindications to implantation include moderate or severe aortic stenosis or dysfunction, presence of ventricular septum defects, left ventricular thrombosis, or significant peripheral arterial disease<sup>[20]</sup>.

The most common complications are limb ischemia, vascular injury, bleeding requiring blood

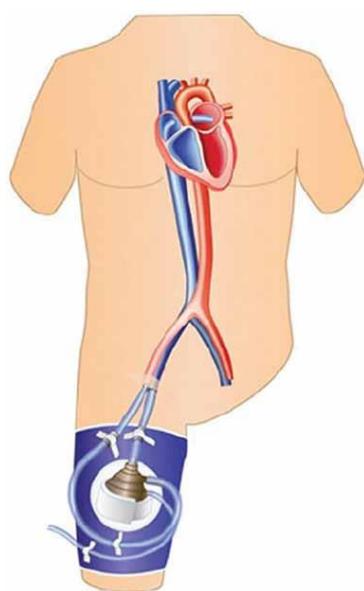
transfusion and hemolysis. There was no significant difference between the safety of ambos and that of intra-aortic counterpulsation balloon<sup>[21]</sup>.



**Figure 2.** Schematic diagram of propulsion system.

### ***Tandem cardiac system® (cardiac assist)***

An external centrifugal pump system has a cannula with an inlet flow at the LA level and a cannula with an outlet flow at the femoral artery level (**Figure 3**). Oxygenated blood pumped into the femoral artery in this way can provide cardiac output of 3.5 to 4.5 L/min. The need for percutaneous puncture increases the risk and complexity of implants. The most common complications are cardiac tamponade, lower limb ischemia, arrhythmias, and persistent septal defects that may require subsequent closure<sup>[22]</sup>.



**Figure 3.** Schematic diagram of series cardiac system.

### ***Extracorporeal membrane oxygenation (ECMO)***

It has been available since 1972 to support heart and lung function because deoxygenated blood is extracted from the body through the cannulas system and then returned to the systematic circulation through the oxygenator. The oxygenator is a gas exchange device that directly oxygenates while removing carbon dioxide from the blood. Blood flow is generated by centrifugal pumps with high blood velocity, generating the least possible trauma to blood components<sup>[20]</sup>, providing continuous, non-pulsatile flow of up to 3.5–4.5 L/min and extracorporeal oxygenation.

If blood is extracted from the central vein and returned to the venous system, the process is called venous-venous ECMO (ECMO-VV); If blood is extracted from the venous system and returned to the arterial system, it is called venous-arterial ECMO (ECMO-VA). In the first case, only respiratory support was provided, while the second is used for cardio-respiratory and in cases such as cardiogenic shock (**Figure 4**). The most common complications include massive hemorrhage, cerebrovascular accident, embolic phenomena, infection and multiple organ dysfunction (**Table 2**):

ECMO-VA: This VAD mode intubation can be performed in the center or periphery. During central intubation, blood is discharged directly from RV and returned to aorta, while during peripheral intubation, blood flow is discharged from venous system (femoral vein or jugular vein) through surgery or Seldinger technology and returned to arterial circulation through carotid artery, axillary artery or femoral artery intubation<sup>[23]</sup>.

ECMO-VV: partial or total lung support is preferred when treating severe respiratory failure and maintaining cardiac function. Both drainage and return tubes are located in the venous system.

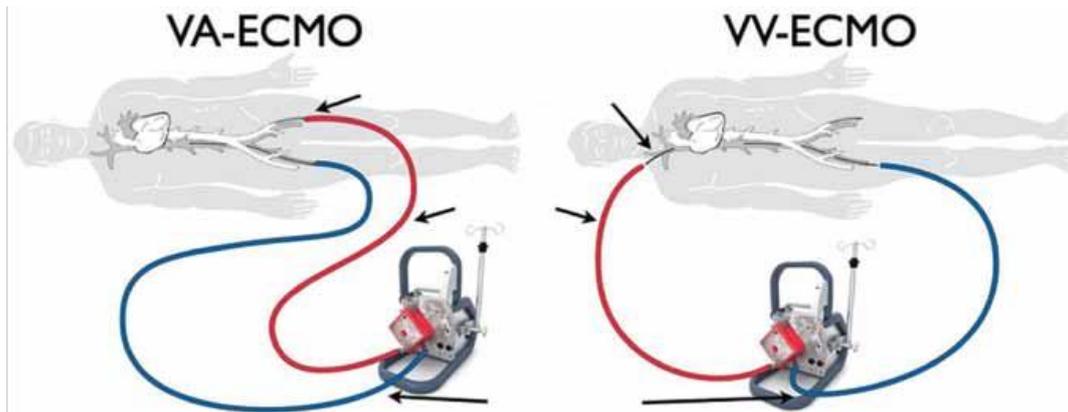


Figure 4. Schematic diagram of extracorporeal membrane oxygenation system: ECMO-VV and ECMO-VA<sup>[23]</sup>.

Table 2. Differences between ECMO modes

Venous artery ECMO	Venous venous ECMO
Achieve higher PaO <sub>2</sub> levels	Reach lower PaO <sub>2</sub> level
Lower infusion rate is required	High perfusion rate
Exclude pulmonary circulation	Maintain pulmonary blood flow
Decreased pulmonary artery pressure	The level of PO <sub>2</sub> in mixed venous blood increased
Provides cardiac support and assists systemic circulation	It provides neither cardiac support nor systemic circulation, and only Requires intravenous intubation
Requires arterial cannulation	Intravenous intubation only

ECMO: ExtraCorporeal membrane oxygenation: extracorporeal membrane oxygenation.

### CentriMag®

It is an extracorporeal centrifugal pump used for surgical implants and can provide blood flow of up to 10 L/min (Figure 5).



Figure 5. A representative of CentriMag.

This is a third-generation continuous pump

with magnetic levitation rotor. It has the least friction, thus reducing the shear force between red blood cells and hemolysis. It has been approved as a support for the left and right ventricles, placing a cannula with inflow at the level of the LV or RV and with the outflow cannula at the level of the aortic or pulmonary artery level, respectively<sup>[25]</sup>. Table 3 summarizes the contraindications and application of short-term VAD.

### 3.2. Long term ventricular assist device

#### Definition

The following definitions are important for understanding the operation and programming of the different devices currently available:

Pump speed (revolutions per minute): determine the speed of the pump flow, and it is programmed in each device according to the patient and medical standards.

Pump flow (L/min): The device flow is directly

proportional to the rotor speed and inversely proportional to the pressure difference between the pump inlet and outlet cannulae; therefore, in addition to the reduction in revolutions per minute, the re-

duction in flow may be caused by various conditions that reduce VAD preload (intravascular volume reduction, RV failure, blockage, inlet cannula blockage).

**Table 3.** Short-term ventricular assist device

Device	Contraindication	Complication
Intra-aortic balloon counterpulsation	Moderate to severe aortic insufficiency. Aortic dissection. Abdominal aortic aneurysm	Thrombocytopenia. Thrombosis, aortic dissection or rupture. Gas embolism.
ECMO	Mechanical ventilation > 7 days.	Circuit thrombosis. Gas embolism. LV dilatation.
Centrimag	Active bleeding.	Thromboembolic events. Gas embolism.
TandemHeart	Ventricular septal defect. Moderate to severe aortic insufficiency. Contraindications to anticoagulation.	Casing displacement. Cardiac tamponade. Thromboembolism. Atrial septal defect.
Impella	LV thrombus Moderate to severe aortic valve disease. Recent TIA/ACV. Contraindications to anticoagulation.	Hemolysis. Device migration. Aortic insufficiency. Ventricular arrhythmia. Cardiac tamponade.
All MCSs	Severe peripheral arterial disease. Sepsis. Contraindications to anticoagulation	Bleeding. Vascular injury. Infected. Nerve injury.

ECMO: Extracorporeal membrane oxygenation. LV: Left ventricle. VAD: Ventricular assist device. TIA/CVA: Transient ischemic attack/cerebrovascular accident.

**Pump power:** It is a measure of the energy and voltage applied to the motor, which changes with the speed and flow of the motor.

**Pulsatility index:** Corresponds to the magnitude of the flow through the pump, it gives the approximate value of the cooperation between LV and the generated flow. It fluctuates with the changes of heart volume and contractility, and the higher the pulsatility, the greater the ventricular preload or contractility.

### Device types

Currently available VAD are divided into three generations according to their development sequence and the type of pumping mechanism used:

(1) First generation or pulsatile flow devices: They were the first to be developed, also known as positive displacement pumps. They are characterized by their large size for patients with medi-

um body surface area. In the design, different parts are exposed to the risk of mechanical failure (valves, inlet and outlet pipelines, etc.). Effectively evacuate the left ventricle and maintain system circulation, with a pumping capacity of up to 10 L/min. Examples of these VAD include: HeartMate I or XVE and Novacor VAD. They were surgically implanted in a pocket under the rectus abdominis or in front of the peritoneum and connected to the left ventricle and ascending aorta<sup>[26]</sup>. In most studies that assessed the maximum support duration has not exceeded 6 months, most were between 50–60 days<sup>[27]</sup>.

(2) Second generation or continuous (axial) flow devices: Much smaller, longer lasting and less complex to implant compared with the first generation. Examples of these devices include: HeartMate 2 VAD (Thoratec Inc.), Jarvik 2000 (Jarvik Heart Inc., New York), Micromed DeBakey VAD and Berlin Heart Incor (Berlin Heart AG). The only moving part of the VAD is the rotor, so its durability

is higher. Its use requires both antiplatelet and anti-coagulant therapy. HeartMate 2 is the second generation of VAD mainly targeted. It was approved as a bridge for transplantation by FDA in 2008 and destination therapy in 2010.

(3) Third generation or continuous flow (centrifugal) device: Small VAD, the rotor is suspended by magnetic force. Examples of this group of

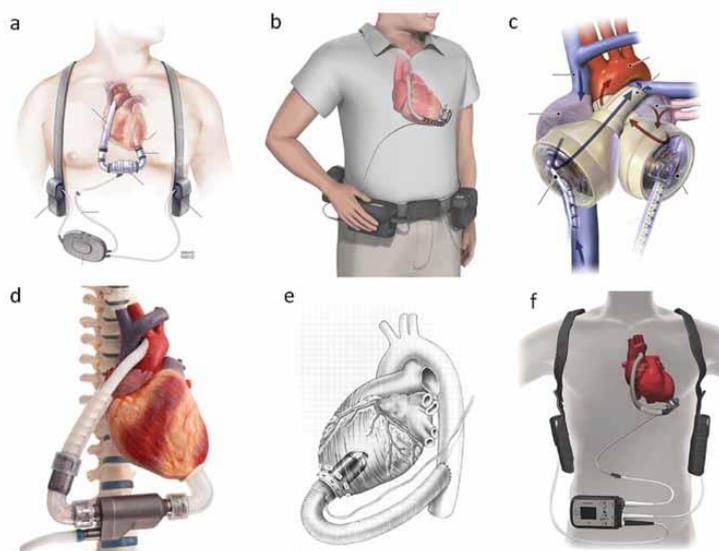
devices are HeartWare and HeartMate III. They are all intracardiac implants, so they do not need to be re-implanted into the abdominal cavity or preperitoneal pocket.

**Table 4** describes the characteristics of long-time VAD, and **Figure 6** shows schematic diagrams of different long-time VAD.

**Table 4.** Characteristics of long-term VAD

Device	Disegno	Operation	Pulsatility	Location of	Weight (g)	Maximum flow (L/min)
HeartMate II	Axial	Mechanical	No	Preperitoneal/intraperitoneal	281	10
Jarvik 2000	Axial	Mechanical	Yes	Pericardium	90	7
Incor	Axial	Hydrodynamic	No	Pericardium	200	8
HeartWare	Centrifugal	Hydrodynamic	No	Pericardium	145	10
HeartMate III	Centrifugal	Magnetic	Yes	Pericardium	200	10

VAD: Ventricular assist device



**Figure 6.** Schematic diagram of long-term ventricular assist device: **a.** HeartMate II LVAD (Thoratec Inc.). **b.** HeartWare LVAD (HeartWare Inc.). **c.** SynCardia total artificial heart. **d.** INCOR (Berlin Heart; Berlin, Germany) and Jarvik, 2000. **f.** HeartMate III (Thoratec Corp)

### **Patient selection**

Candidate patients for MCS are patients with previously defined advanced HF. This definition covers a wide range of patients with different clinical manifestations, severity and prognosis, which is why the INTERMACS group has developed a seven-stage classification to sub-classify these patients (**Table 5**).

For patients with INTERMECS 1 and 2 characteristics, long-term VAD implantation should be avoided because of its low survival rate; instead, they should be considered as short-term equipment. The INTERMACS 3 group was the patient who benefited the most from long-term VAD.

**Table 5.** Classification in 7 stages of patients-INTERMACS profile descriptions

Profile	Description	Characteristics	SCM Type
1	Critical cardiogenic shock	Life-threatening hypotension and the rapid increase in the demand for pressor drugs, insufficient perfusion of key organs, acidosis and deterioration of lactic acid concentration.	Short-term VAD or ECMO-VA
2	Progressive deterioration	Organ function impairment, despite intravenous muscle strength support, is characterized by deterioration of renal function, lack of nutrition and inability to restore volume balance.	Short-term VAD or LVAD
3	Stable but inotrope dependent	Stability of blood pressure, organ function, nutrition and symptoms, continuous intravenous muscle strength support (or VAD), but repeated attempts to withdraw from treatment due to hypotension or renal insufficiency.	LAVD
4	Symptoms at rest with oral home treatment	Daily symptoms of congestion. The dosage of diuretics fluctuates greatly. Consider more rigorous treatment strategies and monitoring. It can oscillate between profile 4 and 5.	LAVD
5	Intolerable movement	He is very comfortable at rest, but he is unable to engage in any activities and can only stay at home.	Consider LAVD
6	Limited exercise capacity	Comfortable at rest, no signs of water overload, able to carry out some minor activities. Activities of daily living are very comfortable. You can visit friends or go out to dinner, but you will be tired in a few minutes.	Consider LAVD
7	NYHA III advanced function class	Clinically stable, with a reasonable level of comfortable activity, with a history of decompensation that is not recent. You can walk more than one block. Any decompensation requiring intravenous diuretics or hospitalization in the last month falls into profile 6.	Not consider LAVD

INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support (NYHA): Interinstitutional registry of mechanically assisted circulatory support. VAD: Ventricular assist device. LVAD: Long-term ventricular assist device.

NYHA: New York Heart Association.

ROADMAP 28 evaluated long-term VAD treatment compared with optimal drug treatment in outpatients and heart failure patients who did not rely on muscle strength therapy (INTERMACS curve  $\geq 4$ ). After one year of follow-up, the survival rate and functional status of patients receiving ventricular care were significantly improved; however, adverse events doubled in this treatment group. The HeartMate II risk score is designed to predict the risk of candidate patients with long-term VAD implantation, whether as a target treatment or as a bridge to HT. Different factors were identified as: Hypoproteinemia, renal failure, experience of implantation center and patient age were risk factors for 90 day mortality<sup>[29]</sup>.

In the eighth annual report of INTERMACS, more than 20,000 patients with long-term VAD implantation in more than 180 hospitals were report-

ed<sup>[30]</sup>. 2,500 devices are implanted each year. In 18,987 cases of implanted LVAD, more than 90% were continuous.

Since 2013, both centrifugal pump and axial flow pump have been put into use. About 50% of the devices are implanted as treatment targets, 26% represent patients waiting for HT examination, and 23% represent patients with bridging strategy. Since 2008, the proportion of patients implanted with VAD during cardiogenic shock has stabilized at 14–16%, of which the largest proportion is patients with contour 3 (stable but requiring muscle strength), accounting for 38% of all implants. Profiles 4 to 7 (considered outpatient CI) have decreased to 12.8% of total implants (**Table 5**).

### **Clinical evidence**

As devices become more durable, portable, and easier to program, and the use of targeted therapy becomes more and more common, long-term

VAD was initially evaluated as a bridge to HT in waiting patients. **Table 6** summarizes the main

clinical studies that evaluated the survival of these devices<sup>[31]</sup>.

**Table 6.** Published clinical studies of left ventricular assist devices

Anal study	N	Device	Instructions	Research design	Patient population	Result
EMATCH, 2001 <sup>[11]</sup>	129	HeartMate XVE	DT	Prospective 1:1 HeartMate XVE vs medical therapy	Patients with CF IV (NYHA) for 60 days, LVEF <25%, peak oxygen consumption <14 ml/min/kg (unless on counterpulsation ball, IV inotrope or physically unable to perform exercise test), or intra-aortic counterpulsation ball or IV inotrope-dependent or intra-aortic balloon pump for 14 days	Survival of 52% and 23% with 1 and 2 years with HeartMate XVE vs 25% and 8% with medical therapy
INTREPID, 2007 <sup>[31]</sup>	55	Novacor	DT	Non-random prospective	Inotrope-dependent patients	Survival of 27% with 1 year with Novacor vs 11% with medical therapy
HeartMate II, 2009 <sup>[12]</sup>	192	HeartMate II	DT	Prospective randomized 2:1 HeartMate II vs HeartMate XVE	In the past 60 days, patients with CF IIIB or IV (NYHA) have more than 45 days, LVEF <25%, maximum oxygen consumption <14 ml/min/kg (unless they have a balloon counterpulsation, inotropes, IV or physically unable to perform exercise testing), or intra-aortic balloon pump or IV inotrope-dependent for 14 days	Survival of 68% and 58% with 1 and 2 years with HeartMate II vs 55% and 24% with HeartMate XVE
HeartMate II post approval, 2014 <sup>[31]</sup>	247	HeartMate II	DT	Non-random prospective	Consecutive patients eligible for DT in INTERMACS	Survival of 74% and 61% with 1 and 2 years with HeartMate II 75% survival to transplant, recovery or continued support, although still eligible for transplant at 6 months
HeartMate II, 2007 <sup>[33]</sup>	133	HeartMate II	BTT	Non-random prospective	Transplant candidates	90% survival to transplant, recovery or continuous support at 6 months
HeartMate II post approval, 2011 <sup>[31]</sup>	169	HeartMate II	BTT	Non-random prospective	Consecutive patients eligible for transplantation at INTERMACS	90.7% survival to transplant, recovery or continuous support with the original device vs 90, 1% in the control group at 6 months
Advance, 2012 <sup>[34]</sup>	137	HVAD	BTT	Non-random prospective HVAD Compared with 499 patients receiving FDA-approved HVAD at INTERMACS	Transplant candidates	90.7% survival to transplant, recovery or continuous support with the original device vs 90, 1% in the control group at 6 months

N: Number of patients. CF: Functional class NYHA: New York Heart Association. BTT: Bridge to transplant. DT: Destination therapy. LVEF: Left ventricular ejection fraction IV: Intravenous injection. FDA: Food and drug administration. HVAD: HeartWare Ventricular Assist Device NTERMACS: Interinstitutional Registry of Mechanical Circulatory Assistance support. INTREPID: Investigation of transplant ineligible patients who are inotrope dependent. LVAD: Left ventricular assist device. REMATCH: Randomized evaluation of mechanical assistance for the treatment of heart failure. ADVANCE: Evaluation of the HeartWare ventricular assist device for the treatment of advanced heart failure

The REMATCH 11 study, published in 2001, is the cornerstone for determining the benefits of long-term VAD treatment in patients with advanced heart failure, although this study shows that the improvement of beyond phase VI, durability and the incidence of complications associated with heart

disease XVE are below optimal levels. Subsequent studies of continuous flow devices (HeartMate II and HeartWare) showed significant benefits in survival between the ages of 32 and 34. In 2010, the FDA approved HeartMate II and began to expand destination therapy in 2012. Since 2012, the number

of implants used for this purpose has exceeded the bridging indications of TC 30. In a prospective, non-randomized study, 10 centers from Europe, Australia and Canada reported the latest evidence of the third-generation device (HeartMate III). In this preliminary trial of 50 patients, the researchers reported a 92% survival rate without stroke or device replacement<sup>[35]</sup>. A study is currently under way to compare the non-inferiority of HeartMate III and HeartMate II as graft bridges or destination therapies.

## 4. Complications of long-term VAD

### 4.1. Thrombosis

In these patients, one cause of the low cardiac output state is device thrombosis, which occurs in about 8% of the implanted continuous flow VAD<sup>[36]</sup>, blocking the input and output cannulas. Thrombosis can occur in the same device or can be dragged from another place into the same device<sup>[37]</sup>. This may occur even in patients who are correctly anticoagulated and antiplatelet due to the chronic hypercoagulable state caused by VAD. The thrombosis of the device can be manifested as cardiogenic shock, and the rough noise generated by the thrombus in the device can be recognized. At the laboratory level, the increase of LDH level can be demonstrated by strong hemolysis. Chest X-rays may show the wrong location of inlet and outlet catheters, or signs of pulmonary congestion with decompensated heart failure. On Doppler echocardiography, left ventricular dilatation, severe mitral insufficiency and frequent aortic valve opening indicate insufficient flow, and this diagnosis should be suspected<sup>[38]</sup>. Anticoagulant therapy, fibrinolytic therapy, equipment replacement or HT optimization can be considered as emergency treatment.

### 4.2. Acute right ventricular failure

It occurs in 5~10% of patients after long-term VAD implantation<sup>[39]</sup>. Suspicious factors of Doppler echocardiography include impaired right ventricular dilation and systolic function, tricuspid insufficiency

and reduced tricuspid annulus offset. In right heart catheterization, pulmonary artery pressure and central venous pressure increased, and pulmonary artery pressure was normal. In terms of treatment, muscle strength drugs such as dobutamine, milrinone or norepinephrine take effect quickly. If medication does not improve symptoms, the right short-term VAD implant should be considered as a rapid propulsion or tandem heart until recovery, or as a bridge to the VD long-term auxiliary implant<sup>[40]</sup>.

### 4.3. Gastrointestinal bleeding

The reported incidence of complications ranged from 22% to 40%<sup>[41]</sup>. It is speculated that the cause of this common complication is the change of blood flow pattern, especially the lack of continuous flow device and acquired von Willebrand factor. The pattern of minimal or zero opening of the aortic valve in these patients is similar to those with severe aortic stenosis (Heyde syndrome), resulting in abnormal pulse curve, insufficient intestinal perfusion, dilation of the submucosal venous plexus of the gastrointestinal tract, resulting in vascular dysplasia, arteriovenous malformations and bleeding.

### 4.4. Infection and sepsis

The infection rate of continuous flow equipment is lower than that of pulse equipment; nevertheless, the infection rate remains a common complication (30–50% of implant devices)<sup>[42]</sup>. VAD patients, as an indication of targeted therapy, are more likely to be infected than HT bridges because they tend to be older, more advanced and take longer ventricular care. The diagnosis and treatment of sepsis are the same as those of the general population.

## 5. Conclusions

HT is still the best treatment for patients with advanced heart failure; however, due to the global donor shortage and long waiting list, given the quality of life of patients with this serious disease, the increasing development and use of VAD has

improved short-term and long-term survival, resulting in a gradual reduction in the rate of complications. These benefits not only provide a choice for patients waiting for HT, but also give those with reversible contraindications the time and opportunity to become suitable candidates or, if impossible, eventually use it as a target treatment. However, these devices have many limitations: their cost, durability, incidence of complications and their limited application. Technological advances in mitigating complications, increased experience in management centers, and their promotion to reduce costs will continue to strengthen the use of VAD in patients with advanced heart failure.

## Conflict of interest

The author declares no conflict of interest.

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