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Implantable ventricular assistance systems (VAD) as a bridge to transplant or as ‘destination therapy’

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Heart failure is a complex clinical syndrome associated with a high mortality and morbidity rate. Despite the extensive pharmacological armamentarium, a non-negligible percentage of patients develop advanced heart failure and require further therapies. In these circumstances, heart transplantation remains the treatment of choice, but the limited number of donors and the reduction of potential candidates have made necessary to develop new technologies. Since the 1980s, left ventricular assist devices (LVADs) have been introduced and have completely revolutionized the landscape of advanced heart failure treatments. This article has identified the categories of patients who can benefit from the implantation of an LVAD and summarized the new classifications. In addition, the main LVADs are described, analysing the results of the main clinical studies, with particular reference to adverse events. Although there is no perfect LVAD, a multidisciplinary team approach, dedicated to the treatment of advanced heart failure, can guide the choices on the best device to implant, in order to minimize complications and improve the patient’s quality of life.

Introduction

Heart failure is defined as a clinical syndrome characterized by typical symptoms (dyspnoea at rest, fatigue, and lower extremities oedema) which may be accompanied by signs (elevated jugular pressure, tachycardia, tachypnoea, pulmonary rales, peripheral oedema, hepatomegaly) caused by an objective structural and/or functional cardiac anomaly that causes a reduction in cardiac output and/or elevated intracardiac pressures at rest or during stress.¹ Heart failure is defined as advanced when, despite maximal medical therapy, severe symptoms of heart failure persist, as well as clinical signs of fluid retention and/or peripheral hypoperfusion, evidence of severe systolic and/or diastolic cardiac dysfunction.

In Western countries, the prevalence of heart failure in adults is ~1-2%; estimating that of the advanced/refractory forms remains, to date, a real epidemiological

challenge: both due to the relatively low incidence, and to the variability between centres in defining the cut-offs for the definition of the disease itself.²

Although the implementation of drug therapies has significantly improved survival and reduced the hospitalization rate of patients, mortality remains substantially high. The most recent data from the US-HF registry show that the 5-year mortality and re-hospitalization rate is 75.4% and 80.4%, respectively.³

Even today, heart transplantation is the gold standard for patients with advanced heart failure; despite this, due to a limited number of donors and long waiting times, left ventricular assist device (LVAD) have become an important therapeutic alternative, both for patients waiting for transplantation (bridge to transplant), and for those not eligible (destination therapy). Recently, three other categories of patients have been included among those who can benefit from left ventricular assistance: those who are waiting for a therapeutic choice (bridge to decision), those who could have a total recovery of cardiac function (bridge to

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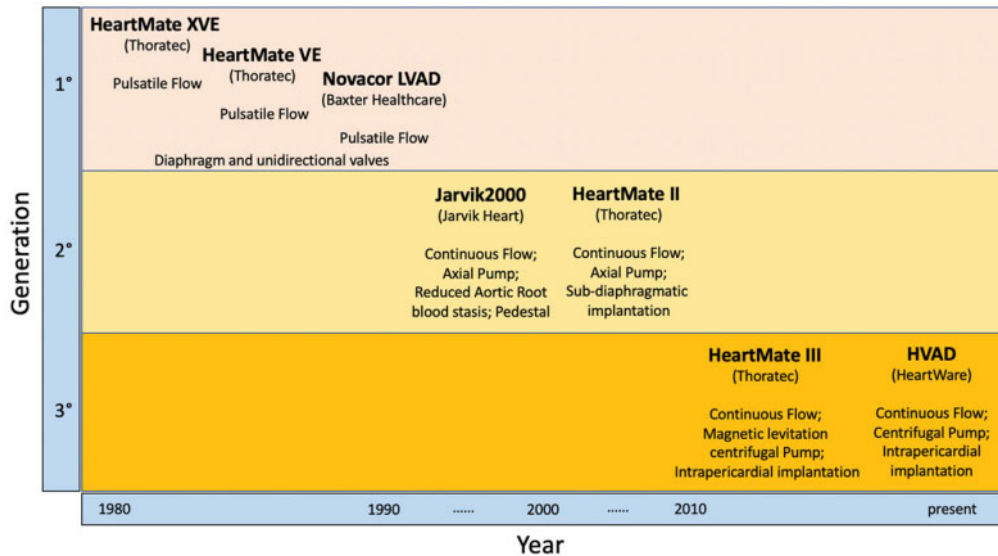


Figure 1 Evolution and principal characteristics of the main left ventricular assist devices. LVAD, left ventricular assist device.

recovery), and finally, those who are temporarily not eligible for transplantation and for whom left ventricular assistance is necessary to improve organ function in order to be candidates for heart transplantation (bridge to candidacy).

In 2009, the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) classification system was introduced which, based on the clinical characteristics of the patient suffering from advanced heart failure, makes it possible to identify those who can benefit most from ventricular assistance. In the early years, LVAD implantation was performed in patients in cardiogenic shock (INTERMACS 1 and 2). Subsequently, attention was focused, above all, on patients in INTERMACS 4-7, that is, patients with heart failure followed on an outpatient basis; the rationale for this choice was that, by intervening before the clinical condition deteriorated, better long-term results could be obtained.

Evolution of left ventricular assist devices

The first left ventricular assistance, approved in 1994 as a bridge to transplant and in 2003 as a destination therapy, was the HeartMate XVE (Thoratec Corp.), a device that replicated the pulsatile flow of the heart (Figure 1). Like other LVADs created in those years (HeartMate VE and Novacor LVAD), it used a diaphragm and one-way valve that allowed blood to move. These devices, however, did not allow long-lasting assistance and, moreover, were large in size.

Numerous randomized, multicentre, and prospective studies have investigated the use of these first-generation devices in patients with heart failure, comparing them with standard medical therapy. In particular, the REMATCH study demonstrated an increase in survival in patients not eligible for transplantation, in INTERMACS Classes 1-3, with LVAD (HeartMate VE) compared to those undergoing optimal medical therapy both at 1 year (52% vs 25%, $P = 0.002$) and at 2 years (23% vs 8%, $P = 0.09$).⁴ Among secondary

outcomes, patients in the LVAD group had a 2.35-fold higher incidence of adverse events, especially bleeding, infections, and device failures.

The subsequent technological development has led to the introduction of continuous flow devices which, compared to their predecessors, have characteristics that have allowed them to be used more widely: small dimensions, reduced weight, relative silence, power supply guaranteed by a percutaneous cable, and improved durability.

Left ventricular assist device design and technology has seen significant advances in recent decades, but the six main components have remained the same: (i) an inflow from the left ventricle to the pump; (ii) an electric motor and a pump positioned within the pericardial or peritoneal space; (iii) a conduit for the outflow from the pump to the aorta; (iv) a percutaneous driveline for power supply; (v) a controller with pump parameters; and (vi) a source of electricity.

In 2001, the HeartMate II (Thoratec Corp.), a small axial pump that could be implanted in the sub-diaphragmatic area, was introduced to the market. Miller *et al.*⁵ evaluated the efficacy of this LVAD in 133 patients awaiting transplant (bridge to transplant). Survival was 89%, 75%, and 68% at 1 month, 6 months, and 12 months, respectively. The results of this study showed that using the device for periods of at least 6 months led to an improvement in the functional status and quality of life.⁵ In a subsequent randomized, multicentre trial, Slaughter *et al.*⁶ compared HeartMate II with HeartMate XVE in 200 patients not eligible for transplantation (destination therapy). The authors reported improved 2-year survival in HeartMate II-treated patients (58% vs 24%, $P = 0.008$).

In the same years another continuous flow device and axial pump were introduced to the market, the Jarvik 2000. Used for the first time in humans in 2000, we now have more than 900 implants as bridge to transplant, bridge to recovery, and destination therapy; the longest support with this LVAD was 9.5 years before heart transplant. The Jarvik 2000 is a versatile device as it can be implanted both

via median sternotomy and through a left thoracotomy by suturing the outflow tract directly into the descending thoracic aorta (useful, e.g. in patients who already had cardiac surgery). In addition, the controller reduces the axial pump speed for 8 s every minute, producing an increase in preload and consequently generating a ventricular ejection volume. This allows to reduce stasis in the aortic root and to provide the circulation with a physiological, even if only temporary, pulsatility. However, the feature that makes this device still widely used is the possibility of having the power cable, not only at the abdominal level, but also in the retroauricular area. This system, called retroauricular pedestal, allows the connection of the power cable and the battery through a connector fixed at the level of the temporal-parietal area of the skull.⁷

The problem of infections in LVAD patients represents an important issue, and it was necessary to arrive at shared definitions; in this regard, in 2010, the International Society for Heart and Lung Transplantation (ISHLT) Infectious Disease Working Group was instituted, which divided infections in this category of patients into three groups: specific LVAD infections, LVAD-related infections, and infections not LVAD relate. Among the specific LVAD infections, those of the driveline, considered the most common, have been classified as certain, probable, or possible, superficial or deep.

In this regard, the use of the retroauricular pedestal in Jarvik 2000, due to its system characteristics, represents a valid option. Some studies in the literature, in fact, have shown a lower rate of infections of the retroauricular driveline compared to the abdominal one and the rationale is based on the fact that (as for dental and cochlear implants) the bone tissue, for its vascularization and for the ability to minimize driveline movements, is less prone to infections. On the subject, Siegenthaler *et al.* published a retrospective study comparing 11 patients with HeartMate II and 6 patients with Jarvik 2000. In the HeartMate group, 7 (64%) were reported driveline infections, 5 (45%) were reported device pocket infections, and 3 (27%) were reported bloodstream infections; moreover, the onset of infections was quite early (34 ± 31 days). In the Jarvik 2000 group, only one driveline infection (16%) was reported 270 days after implantation, significantly lower than in the HeartMate group ($P = 0.044$). Additionally, the Jarvik group received fewer antibiotics ($P = 0.039$), with significantly higher cost for antibiotics in the HeartMate group ($P = 0.018$).⁸

The third generation of LVAD is mainly represented by two centrifugal pump devices: HeartMate 3 (St. Jude, Abbott) and HVAD (HeartWare, Medtronic). These LVADs are so small that they can be implanted intrapericardially. In addition, the pump impeller is equipped with a total magnetic levitation and/or hydrodynamic levitation system that minimizes thrombosis and haemolysis due to the reduction of wall stress and the degradation of coagulation factors.

Numerous studies have been published in recent years to validate the effectiveness of these new devices. The ADVANCE trial, conducted on 140 subjects undergoing HVAD implantation, showed the non-inferiority of this LVAD to the devices commercially in use in those years, comparing the data from the population of the INTERMACS

registry.⁹ The control group included almost exclusively patients (499) who had been implanted with an LVAD with an axial continuous flow pump. The results of the study showed a success rate of 90.7% for HVAD and 90.1% for the control group, thus establishing the non-inferiority of HVAD ($P < 0.001$; 15% non-inferiority margin). Subsequently Rogers *et al.*¹⁰ published data from the ENDURANCE trial, a prospective, randomized, multicentre study. The comparison between HVAD and the second-generation HeartMate II device demonstrated the non-inferiority of the new HVAD on 2-year survival (55.4% vs 59.1%, respectively, $P = 0.01$) in the absence of stroke or removal of the device for malfunction or dysfunction.

In addition to infections, haemorrhagic/thrombotic complications remain the Achilles' heel of these devices, contributing significantly to the morbidity and mortality associated with their use. Some recent studies have specifically investigated these aspects. For example, Jarvik 2000 has been shown to significantly reduce the number of platelets, thus compensating for the intrinsic thrombogenicity of the axial pump; this phenomenon, however, is not present in patients who have been implanted with HVAD. Knowledge and understanding of these results are very important, especially for the correct management of antiplatelet or anticoagulant therapy.¹¹ Mondal *et al.*¹² compared the presence of intraplatelet oxygen free radicals, mitochondrial damage, and platelet apoptosis after implantation of HeartMate II, Jarvik 2000, and HeartWare. The results showed minimal mitochondrial damage in HeartMate II and Jarvik 2000 patients, while in the HeartWare group there was more severe damage and also increased platelet apoptosis. These data could explain the major bleeding complications both in the immediate post-operative period and the incidence of gastrointestinal bleeding found in this group compared to the other two.

The new LVAD on the market, the HeartMate 3, received the CE mark in 2015 following the multicentre study conducted by Netuka *et al.*¹³ The trial included 50 patients, of which 54% as bridge to transplant and 46% as destination therapy; the primary endpoint was 6-month survival and the results were compared with patients in the INTERMACS registry undergoing HeartMate II implantation. At 6 months, 88% of patients still needed support, 4% had received a heart transplant and 8% had died. Survival at 6 months was 92%, better than that derived from the INTERMACS registry data. In 2019, Mehra *et al.*¹⁴ published the 2-year results of a multicentre, randomized comparison study between HeartMate 3 and HeartMate II called MOMENTUM 3. The trial enrolled 1028 patients (bridge to transplant and destination therapy), 516 received HeartMate 3 and 512 the HeartMate II. Results demonstrated non-inferiority and superiority of HeartMate 3 with respect to the primary composite endpoint of 2-year survival, freedom from disabling stroke, or reoperation to replace or remove a malfunctioning device (76.9% for HeartMate 3 vs 64.8% of HeartMate II, $P < 0.001$). In addition, device thrombosis (and subsequent replacement surgery) occurred in 12 patients in the HeartMate 3 group (2.3%) and in 57 (11.3%) in the HeartMate II group ($P < 0.001$). Other adverse events were greater in HeartMate II patients, such as stroke (19.4% vs 9.9%, $P < 0.0001$) and

major bleeding (55% vs 43.7%, $P < 0.0001$). Despite this, driveline infection was very common in both groups analysed, with a percentage of 23.8% in the HeartMate 3 group and 19.8% in the HeartMate II group ($P = 0.37$).

In 2021, Schmitto *et al.* published the first 5-year results of patients who underwent HeartMate 3 implant, with a survival of 100% and a significant increase in quality of life; the study demonstrated excellent haemocompatibility of the device, with a low complication rate (haemolysis, pump thrombosis, malfunction, neurological events) probably due to magnetic levitation technology. Also in this study, the most frequent complication was infection of the driveline with a value of 0.25 events/patient-year.¹⁵

Conclusions

Advanced heart failure is a complex syndrome, whose treatment of choice remains heart transplant. However, recent technological advances in LVADs have made it possible to completely revolutionize the treatment of these patients, increasing their life expectancy.

Currently, the most implanted LVADs in the world are second and third generation ones. Despite the benefits that LVADs can bring compared to medical therapy alone, important issues related to bleeding, cerebrovascular events, infections, and thrombosis of the device represent a limitation for these therapies. In particular, the high rate of infections of the device, but above all of the driveline, remains a much debated topic and one of the most frequent complications.

Although there is no perfect LVAD, the characteristics of each device have made it possible to evaluate, on each individual patient, based on the clinical characteristics and the type of indication which LVAD to implant. For example, the versatility of the Jarvik 2000, although it is a second-generation pump, allows for excellent use in patients in destination therapy (reduced rate of the retroauricular pedestal infections and good quality of life).

This patient-tailored approach lends itself perfectly to this type of pathology and treatment. It must necessarily include a multidisciplinary team, made up of various health professionals such as interventional and clinical cardiologists, cardiac surgeons, cardiac anaesthesiologists, and dedicated nurses. The team approach is the main point of LVAD programs, essential not only for the correct selection of the patient, but also to provide adequate technical, pharmacological, and psychosocial assistance not only while waiting for a definitive therapy as transplantation, but even in the long-term support. Furthermore, the choice of the type of device, based on its characteristics, integrated with the patient's clinical ones, will allow to reduce adverse events and manage them, always keeping the patient at the centre of our efforts.

Conflict of interest: none declared.

References

- Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V-P, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;**37**:2129-2200.
- Truby LK, Rogers JG. Advanced heart failure: epidemiology, diagnosis, and therapeutic approaches. *JACC Heart Fail* 2020;**8**:523-536.
- Severino P, Mather PJ, Pucci M, D'Amato A, Mariani MV, Infusino F, Birtolo LI, Maestrini V, Mancone M, Fedele F. Advanced heart failure and end-stage heart failure: does a difference exist. *Diagnostics (Basel)* 2019;**9**:170.
- Rose EA, Gelijns AC, Moskowitz AJ, Heitjan DF, Stevenson LW, Dembitsky W, Long JW, Ascheim DD, Tierney AR, Levitan RG, Watson JT, Meier P, Ronan NS, Shapiro PA, Lazar RM, Miller LW, Gupta L, Frazier OH, Desvigne-Nickens P, Oz MC, Poirier VL; Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) Study Group. Long-term use of a left ventricular assist device for end-stage heart failure. *N Engl J Med* 2001;**345**:1435-1443.
- Miller LW, Pagani FD, Russell SD, John R, Boyle AJ, Aaronson KD, Conte JV, Naka Y, Mancini D, Delgado RM, MacGillivray TE, Farrar DJ, Frazier OH; HeartMate II Clinical Investigators. Use of a continuous-flow device in patients awaiting heart transplantation. *N Engl J Med* 2007;**357**:885-896.
- Slaughter MS, Rogers JG, Milano CA, Russell SD, Conte JV, Feldman D, Sun B, Tatooles AJ, Delgado RM, Long JW, Wozniak TC, Ghumman W, Farrar DJ, Frazier OH. Advanced heart failure treated with continuous-flow left ventricular assist device. *N Engl J Med* 2009;**361**:2241-2251.
- Selzman CH, Koliopoulou A, Glotzbach JP, McKellar SH. Evolutionary improvements in the Jarvik 2000 left ventricular assist device. *ASAIO J* 2018;**64**:827-830.
- Siegenthaler MP, Martin J, Pernice K, Doenst T, Sorg S, Trummer G, Friesewinkel O, Beyersdorf F. The Jarvik 2000 is associated with less infections than the HeartMate left ventricular assist device. *Eur J Cardiothorac Surg* 2003;**23**:748-754.
- Aaronson KD, Slaughter MS, Miller LW, McGee EC, Cotts WG, Acker MA, Jessup ML, Gregoric ID, Loyalka P, Frazier OH, Jeevanandam V, Anderson AS, Kormos RL, Teuteberg JJ, Levy WC, Naftel DC, Bittman RM, Pagani FD, Hathaway DR, Boyce SW. Use of an intrapericardial, continuous-flow, centrifugal pump in patients awaiting heart transplantation. *Circulation* 2012;**125**:3191-3200.
- Rogers JG, Pagani FD, Tatooles AJ, Bhat G, Slaughter MS, Birks EJ, Boyce SW, Najjar SS, Jeevanandam V, Anderson AS, Gregoric ID, Mallidi H, Leadley K, Aaronson KD, Frazier OH, Milano CA. Intrapericardial left ventricular assist device for advanced heart failure. *N Engl J Med* 2017;**376**:451-460.
- Tarzia V, Buratto E, Bortolussi G, Gallo M, Bejko J, Bianco R, Bottio T, Gerosa G. Hemorrhage and thrombosis with different LVAD technologies: a matter of flow? *Ann Cardiothorac Surg* 2014;**3**:582-584.
- Mondal NK, Sorensen EN, Feller ED, Pham SM, Griffith BP, Wu ZJ. Comparison of intraplatelet reactive oxygen species, mitochondrial damage, and platelet apoptosis after implantation of three continuous flow left ventricular assist devices: HeartMate II, Jarvik 2000, and HeartWare. *ASAIO J* 2015;**61**:244-252.
- Netuka I, Sood P, Pya Y, Zimpfer D, Krabatsch T, Garbade J, Rao V, Morshuis M, Marasco S, Beyersdorf F, Damme L, Schmitto JD. Fully magnetically levitated left ventricular assist system for treating advanced HF: a multicenter study. *J Am Coll Cardiol* 2015;**66**:2579-2589.
- Mehra MR, Uriel N, Naka Y, Cleveland JC, Yuzefpolskaya M, Salerno CT, Walsh MN, Milano CA, Patel CB, Hutchins SW, Ransom J, Ewald GA, Itoh A, Raval NY, Silvestry SC, Cogswell R, John R, Bhimaraj A, Bruckner BA, Lowes BD, Um JY, Jeevanandam V, Sayer G, Mangi AA, Molina EJ, Sheikh F, Aaronson K, Pagani FD, Cotts WG, Tatooles AJ, Babu A, Chomsky D, Katz JN, Tessmann PB, Dean D, Krishnamoorthy A, Chuang J, Topuria I, Sood P, Goldstein DJ. A fully magnetically levitated left ventricular assist device—final report. *N Engl J Med* 2019;**380**:1618-1627.
- Schmitto JD, Mariani S, Li T, Dogan G, Hanke JS, Bara C, Pya Y, Zimpfer D, Krabatsch T, Garbade J, Rao V, Morshuis M, Beyersdorf F, Marasco S, Netuka I, Bauersachs J, Haverich A. Five-year outcomes of patients supported with HeartMate 3: a single-centre experience. *Eur J Cardiothorac Surg* 2021;**59**:1155-1163.