Left Ventricular Assist Devices in the Management of Heart Failure

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Abstract

Mechanical circulatory support has emerged as an important therapy for advanced heart failure, with more than 18,000 continuous flow devices implanted worldwide to date. These devices significantly improve survival and quality of life and should be considered in every patient with end-stage heart failure with reduced ejection fraction who has no other life-limiting diseases. All candidates for device implantation should undergo a thorough evaluation in order to identify those who could benefit from device implantation. Long-term management of ventricular assist device patients is challenging and requires knowledge of the characteristic complications with their unique clinical presentations.

Keywords

Ventricular assist device, complication, patient selection, advanced heart failure, mechanical circulatory support

Disclosure: Edo Y. Birati received research and fellowship support from HeartWare Ltd. Mariell Jessup has no relevant disclosures.
Received: 23 February 2015 **Accepted:** 4 March 2015 **Citation:** *Cardiac Failure Review*, 2015;**1**(1):25–30
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Heart failure (HF) is a leading cause of morbidity and mortality worldwide, affecting 1–2 % of the adult population in western countries with incidence of 5–10 per 1000 persons per year.[1,2] It is estimated that the prevalence of HF will continue to increase as the population ages and, according to the American Heart Association (AHA), by the year 2030 the prevalence of HF in the US alone will rise to over 8 million patients, representing a 25 % increase compared to the year 2010.[3] HF is one of the common causes for hospitalisation, representing 1–2 % of all hospital admissions and the leading reason for admission in individuals above 65 years of age.[4–6]

HF is a progressive disease[7] with approximately 5 % of HF patients suffer from end-stage disease refractory to medical therapy.[8,9] The Heart Failure Association of the European Society of Cardiology (ESC) defined advanced HF as a state in which patients have significant cardiac dysfunction with severe HF symptoms, such as dyspnoea and/or fatigue, occurring at rest or with minimal exertion (NYHA functional class III or IV) despite maximal medical and device (cardiac resynchronisation therapy) therapy.[10] In addition to the aforementioned symptoms, patients with advanced HF usually have objective measurements of peak VO_2 (oxygen uptake) <14mL/kg/min, a 6-minute walk distance <300 meters, and poor cardiac function.[10,11] The prognosis of patients with advanced HF is dismal, with life expectancy of less than two years.[11,12] At this stage, advanced therapies are considered, including heart transplantation, continuous inotropic therapy, mechanical circulatory support or hospice.[1,10,11] Heart transplantation remains the preferable therapy for advanced HF, but the number of transplants done worldwide is trivial compared to demand.[13] Thus, durable mechanical circulatory support (MCS) devices have emerged as an important therapy for advanced HF.[13,14] To date, over 18,000 continuous flow devices have been implanted worldwide.[13,14] In the US alone, 131 hospital centres are approved to implant permanent MCS devices, demonstrating the staggering expansion of MCS as a therapeutic option for end-stage HF.[15]

The Nomenclature of MCS

A ventricular assist device (VAD) is a MCS device that is used to partially or completely support the function of a failing heart. Left ventricular assist devices (LVAD) pump blood from the left ventricle and transfer it to the ascending aorta. LVADs may be used as a bridge to transplant (BTT) for candidates awaiting heart transplantation; as destination therapy (DT) for patients who are not candidates for transplantation; as a bridge to decision for patients too sick to survive the transplant evaluation (so that their suitability for transplantation has not been determined at the time of VAD implantation) and as a bridge to recovery for selected patients who might recover their cardiac function. The latter patients are mostly those with acute cardiomyopathies (ie. fulminant lymphocytic myocarditis, peripartum cardiomyopathy, etc).[11] Interestingly, according to the Sixth annual report of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) the proportion of patients treated with LVAD as DT in the United Sates has increased from 14.7 % in 2006–7 to 41.6 % in 2011–13.[14]

The first-generation VADs had pulsatile flow, designed to mimic the normal function of the heart. These devices were shown to increase survival and quality of life (QoL) of patients with end-stage HF compared to optimal medical therapy (OMT).[16] The second and third generation devices currently in use (primarily HeartMate II, Thoratec Corp. and HVAD, HeartWare Ltd., see *Figure 1*), have continuous flow patterns, and can generate up to 10 litres/minute. Although these devices generate continuous flow, pulsatility may still be present in some patients since the flow delivered by the device is modified by native left ventricular (LV) contractility. Nevertheless, some studies suggest that pulsatile flow is not necessary for adequate perfusion of the end organs.[17]

In the 'HeartMate II' trial, treatment with continuous-flow HeartMate II devices as DT was associated with improved survival compared to

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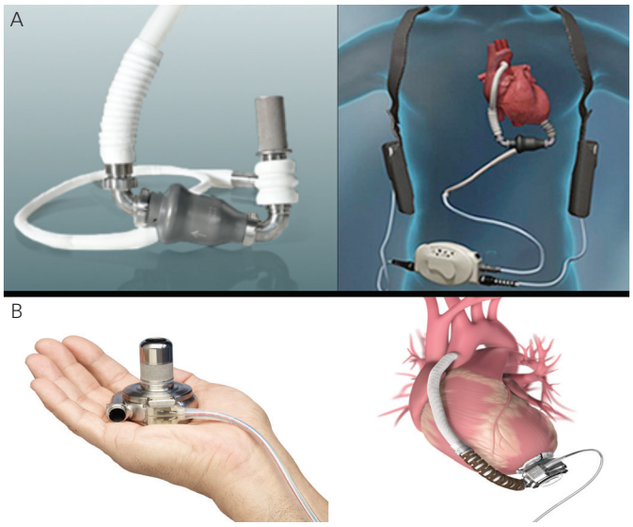
Figure 1: Second and Third Generation Devices Currently in Use



A. HeartMate II device; B. HeartWare HVAD. A. Courtesy of Thoratec, Pleasanton, CA; with permission; B. Courtesy of HeartWare, Framingham, MA.

Table 1: American Heart Association Recommendations for Mechanical Circulatory Support

	Class of Rec.
MCS for BTT indication should be considered for transplant-eligible patients with end-stage HF who are failing optimal medical, surgical, and/or device therapies and at high risk of dying before receiving a heart transplantation.	I
Implantation of MCS in patients before the development of advanced HF (ie, hyponatraemia, hypotension, renal dysfunction, and recurrent hospitalisations) is associated with better outcomes. Therefore, early referral of advanced HF patients is reasonable.	IIa
MCS with a durable, implantable device for permanent therapy or DT is beneficial for patients with advanced HF, high one-year mortality resulting from HF, and the absence of other life-limiting organ dysfunction; who are failing medical, surgical, and/or device therapies; and who are ineligible for heart transplantation.	I
Patients who are ineligible for heart transplantation because of pulmonary hypertension related to HF alone should be considered for bridge to potential transplant eligibility with durable, long-term MCS.	IIa
Careful assessment of RV function is recommended as part of the evaluation for patient selection for durable, long-term MCS.	I
Long-term MCS is not recommended in patients with advanced kidney disease in whom renal function is unlikely to recover despite improved haemodynamics and who are therefore at high risk for progression to renal replacement therapy.	III
Evaluation of potential candidates by a multidisciplinary team is recommended for the selection of patients for MCS	I

BTT = bridge to transplant; HF = heart failure; DT = destination therapy; MCS = mechanical circulatory support; Rec. = Recommendation; RV = right ventricle. Adapted from Peura JL, et al.[11] and published with the permission of the American Heart Association.

pulsatile-flow devices.[18] In addition, patients treated with continuous flow-devices as DT had a significant reduction in the rate of adverse events and hospitalisations and had improved QoL and functional capacity compared to patients treated with pulsatile-flow devices.[18]

To evaluate whether 'real life' outcomes are similar to those observed in the clinical trials, Jorde et al.[19] followed the first 247 patients treated with HeartMate II devices as DT who were not in a clinical trial and compared their outcome with those achieved in the clinical trials. Survival in the later group trended to be better than in the initial clinical trial, with an absolute difference of 74 % versus 68 % at 1 year and 61 % versus 58 % at 2 years (p=0.2). Moreover, the rate of survival free of stroke (both haemorrhagic and ischaemic), device-related infection, or pump replacement was significantly higher in patients treated in the later group.[19] These results are consistent with the outcomes summarised in the Sixth INTERMCAS annual report of 80 % 1-year survival and 70 % 2-year survival.[14]

Treatment with the HeartWare HVAD device as a bridge to transplantation (BTT) was evaluated in the ADVANCE (HeartWare Ventricular Assist Device Bridge to Transplant) trial.[20] In this study, the HeartWare HVAD device was compared to 'commercially available devices', mainly HeartMate II, in patients awaiting heart transplantation. The HVAD device was non-inferior to the HeartMate device with 1-year survival of 86 % and enhanced QoL and functional capacity similar to what was seen with the HeartMate II.[20] The safety and effectiveness of HeartWare HVAD as DT is being evaluated in the ENDURANCE trial, yet to be published.

Patient Selection

LVAD therapy should be considered in every patient with end-stage systolic (low LV ejection fraction) HF who has no other life-limiting diseases. *Tables 1* and *2* summarise the current MCS recommendation from the AHA and the ESC. *Table 3* details the indications and contraindication for MCS.

A MCS evaluation is essential to identify those patients who could benefit from device implantation, and to exclude those considered futile for device therapy. The first step in patient selection is to accurately estimate the clinical severity of the HF syndrome. Many US clinicians[22] recommend the use of two prognostic scores, the Heart Failure Survival Score[23] and the Seattle Heart Failure Model,[24] to estimate the expected two-year survival on medical therapy in candidates who might benefit from LVAD support.[22] The ESC recommend assessing the patient's prognosis using variables that have been shown to predict outcome, such as findings in history and physical examination (NYHA class, blood pressure, signs of congestions, etc.), laboratory tests (serum sodium, liver enzymes, troponins, etc.), neuro-hormonal activity (Plasma renin activity, Angiotensin II, etc.), and functional (peak VO2) and haemodynamic variables.[10,21] Likewise, it is now apparent that there are many phenotypes of advanced HF, which have been described with the INTERMACS profiles, a classification of 7 clinical profiles (see *Table 4*).[25] Patients with INTERMACS profile 1 to 3 are being managed with temporary mechanical or inotropic support, whereas patients with profile 4 to 7 are not inotrope dependent.[11,25] The INTERMACS profiles have been shown to provide prognostic information and guidance for the optimal timing and the associated risk of implantation.[26,27] For example, INTERMACS profile 1 or 2 patients who are treated with LVAD have a 44 % higher post-implantation mortality than that of patients at INTERMACS profile 3 or 4.[27] In addition, several risk scores have been developed for the estimation of short-term mortality after LVAD implantation.[11,22] The 'Lietz-Miller score' was the most frequently used risk score for DT patients (see

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Table 2: European Society of Cardiology Recommendations For Mechanical Circulatory Support

	Class of Rec.
An LVAD or BiVAD is recommended in selected patients with end-stage HF despite optimal pharmacological and device treatment and who are otherwise suitable for heart transplantation, to improve symptoms and reduce the risk of HF hospitalisation for worsening HF and to reduce the risk of premature death while awaiting transplantation.	I
An LVAD should be considered in highly selected patients who have end-stage HF despite optimal pharmacological and device therapy and who are not suitable for heart transplantation, but are expected to survive >1 year with good functional status, to improve symptoms, and reduce the risk of HF hospitalisation and of premature death.	IIa

Rec. = Recommendation; HF = Heart failure; LVAD = left ventricular assist device; BiVAD = bi-ventricular assist device. Adapted from McMurray et al.[21] with the permission of Oxford University Press (UK), © European Society of Cardiology, www.escardio.org/guidelines

Table 3: Indication and Contra-indication for Durable Mechanical Circulatory Support

Indications	Absolute Contraindications
Frequent hospitalisations for HF	Irreversible hepatic disease
Intolerance to neurohormonal antagonists	Irreversible renal disease
NYHA IIIb–IV functional limitations despite OMT	Irreversible neurological disease
End-organ dysfunction owing to low CO	Medical nonadherence
Increasing diuretic requirement	Severe psychosocial limitations
CRT nonresponder	
Inotrope dependence	
Low peak Vo_2 (<14mL/kg/min)	

HF = Heart failure; OMT = optimal medical therapy; NYHA = New York Heart Association; CO = cardiac output; CRT = cardiac resynchronisation therapy. Adapted from Peura et al.[11] and published with the permission of the American Heart Association.

Table 5)[28], but is now limited in use as it was developed on the first generation HeartMate XVE device.[28]

The second step in the evaluation is to search for significant co-morbidities and other factors that might limit the patient's suitability.[11] This search should include the possibility of reversible causes of heart failure (for example: obstructive sleep apnoea), metabolic stress testing when feasible (stress tests are contra-indicated in patients on inotropes), invasive haemodynamic evaluation, laboratory evaluation of organ function including lungs (pulmonary function tests), renal, liver, and haematologic function. All patients should undergo a psychosocial evaluation to estimate patient psychological status, risk for substance abuse, compliance to treatment and supporting environment.[22,29]

Right ventricular (RV) failure is a leading cause of mortality after LVAD implantation,[22] since LVAD optimal function relies on adequate filling of the left ventricle (LVAD preload), which in turn is dependent on RV function. Many studies have tried to predict which patients are at risk for RV failure after LVAD implantation.[30–36] *Table 6* summarises the major published predictors of post implant RV failure.

The final step in evaluating LVAD candidates is an estimation of a patient's overall frailty. Frailty was originally a geriatric term defined as a state of vulnerability to adverse outcomes and decreased physiologic reserve, reflecting the biologic rather than chronologic age.[37,38] Frailty is very common among HF patients and adversely affects prognosis[39,40]. In LVAD patients, frailty is associated with higher post-implant complication rates and mortality.[38,41]

Table 4: INTERMACS Profiles

Profiles	Brief Description	Details
INTERMACS 1	Critical cardiogenic shock (Crash and burn)	Life-threatening hypotension despite rapidly escalating inotropic support.
INTERMACS 2	Progressive decline (Sliding fast on inotropes)	Declining function despite intravenous inotropic support.
INTERMACS 3	Stable but inotrope dependent (Dependent stability)	Stable on continuous intravenous inotropic support.
INTERMACS 4	Resting symptoms on oral therapy at home	Patient experiences daily symptoms of congestion at rest or during activities of daily living.
INTERMACS 5	Exertion intolerant	Patient is comfortable at rest and with activities of daily living but unable to engage in any other activity.
INTERMACS 6	Exertion limited (Walking wounded)	Patient has fatigue after the first few minutes of any meaningful activity.
INTERMACS 7	Advanced NYHA class III (Placeholder)	Patients living comfortably with meaningful activity limited to mild physical exertion.

INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support; NYHA = New York Heart Association. Adapted from: Stevenson LW, et al.[25]

Table 5: Risk Factors for Post-implant 90-Day Survival The Lietz Model

Risk Factor	Score	Risk Category	90-day Survival
Platelet <148x103/µl	7	Very high risk >19	17.9 %
Alb ≤3.3 g/dL	5		
INR > 1.1	4	High risk – 17–19	38.9 %
Vasodilator therapy	4		
Mean PAP ≤25 mm Hg	3	Medium risk: 9–16	86.5 %
AST > 45 U/mL	2		
Hct ≤34 %	2		
BUN >51 U/dL	2	Low risk <9	93.7 %
No IV inotropes	2		

INR = International normalisation ratio; alb = albumin; PAP = pulmonary artery pressures; AST = Aspartate aminotransferase; Hct = Haematocrit; BUN = Blood urea nitrogen; IV = intravenous. Adapted from Lietz K, et al.[28]

LVAD Complications

Patients treated with long-term MCS may develop characteristic complications associated with the implantation of the VAD.

VAD Thrombosis

VAD thrombosis, one of the most devastating complications of MCS, is defined as the development of a blood clot within one component of the device, including the inflow cannula, outflow cannula, and the rotor despite anticoagulation and antiplatelet therapy.[42] Since 2011, for unknown reasons, there has been a reported abrupt increase in the incidence of HeartMate II VAD thrombosis from 2.2 % before 2011 to 8.4 % in 2013.[42] Device thrombosis is also a complication in

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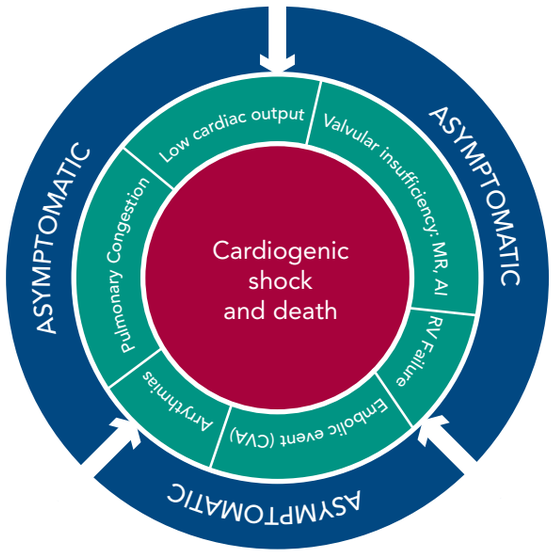
Table 6: Pre-implant Predictors of Acute Right Ventricle Failure

		Comment
Echocardiographic findings	RVEDV > 200 ml RVESV > 177 ml RV free wall strain RV fractional area change RV volumes assessed by 3D	
Laboratory	Bilirubin > 2mg/dl AST >80 IU, Creatinine > 2.3mg/dl WBC > 10.4X103/mL Haematocrit <31 %	
Haemodynamics	PVR >4 woods unit TPG>15 mmHg CVP >15 mmHg RVSWI < 300 mmHg.ml/m^2 CVP / PCWP ratio >0.63	RVSWI<600 – 38 % risk of RV failure RVSWI > 900 – 3 % risk for RV failure.
Clinical	On vassopressors Pre-op mechanical ventilation	Need for vassopressors

RVEDV = Right ventricle end diastolic volume; RVESV = Right ventricle end systolic volume; RV = right ventricle; AST = aspartate aminotransferase; WBC = white blood count; PVR = pulmonary vascular resistance; TPG = trans-pulmonary gradient; CVP = central venous pressure; RVSWI = Right ventricle stroke work index. Equal to the stroke volume index multiplied by the difference between the mean pulmonary artery pressure and the mean right pressure.[30–36]

Figure 2: The Clinical Presentation of Ventricular Assist Device Thrombosis



MR = Mirtal regurgitation; AI = Aortic insufficiency; CVA = Cerebrovascular accident; RV = Right ventricle. Adapted from Birati EY, et al.[45]

HeartWare HVAD devices, reported to occur in 8.1 % of the patients.[43] However, unlike the increase in the incidence of HeartMate II VAD thrombosis, the incidence of HeartWare HVAD thrombosis has remained stable since 2008.[43,44] With the growth in the number of patients treated with LVAD, the magnitude of this complication will continue to rise if there is no deployable strategy to mitigate the risk of pump thrombosis.[45]

VAD thrombosis has more than one clinical presentation, and can involve a wide spectrum of clinical features, ranging from an asymptomatic patient to one with refractory cardiogenic shock and subsequent death.[45] The various clinical presentations are detailed in *Figure 2*. Even early stages of VAD thrombosis may cause haemolysis that can be identified with elevated lactate dehydrogenase (LDH) levels, indirect bilirubin and plasma free haemoglobin (PFHg) levels.[22] Uriel et al.[46] reported that an LDH higher than five times normal was 100 % sensitive and 92 % specific for the diagnosis of pump thrombosis[46], but our series argue that any value above the normal LDH range can imply VAD thrombosis.[45]

Patients with a suspected diagnosis of VAD thrombosis should be started on intravenous heparin, unless contraindicated; patients with highly suspected VAD thrombosis should be considered for pump exchange.[47] Starling et al.[42] showed that the six-month mortality of HeartMate II patients treated with device replacement was similar to the mortality of patients who did not have pump thrombosis.[42] In patients with HeartWare HVAD thrombosis it is reasonable to start thrombolysis if the patient is haemodynamically stable and has no contraindications for thrombolytic therapy. However, if the HVAD patient does not improve clinically or suffer from haemodynamic instability, pump replacement should be considered.[47]

Acute Right Ventricular Failure

Acute RV failure is a frequent complication, occurring in 20–50 % of patients following LVAD implantation, and is associated with increased morbidity and mortality.[48–50] Acute RV failure post-LVAD implantation is defined as a need for inotropes longer than 14 days after LVAD implant or the need for temporary RVAD placement after LVAD surgery.[48,51]

After LVAD placement, there is an abrupt decrease in the left ventricular end-diastolic pressure (LVEDP), followed by a decrease in left pulmonary capillary wedge pressure. In most patients this, in turn, causes a decrease in the pulmonary vascular resistance (PVR), thus decreasing the afterload of the right ventricle.[52] However, some patients have a significant shift of the inter-ventricular septum towards the LV secondary to the decrease in the LVEDP and LV size and consequently an increase in RV preload. This shift of the septum adversely affects the function of the RV. High device speeds enhance this inter-ventricular septum shift, and can further deteriorate the RV function. Thus, it is highly recommended to conduct repeat echocardiographic studies during the first days after the implantation and to adjust the pump speed according to the septal movement and the ventricles size. RV failure can result in inadequate filling of the LV. Since the LVAD is preload dependent, patients with acute RV failure may present with cardiogenic shock.

Up to 15 % of patients with acute RV failure will require RVAD implantation.[53] These patients suffer from severe RV failure leading to end organ dysfunction and cardiogenic shock refractory to inotropes.[53]

In an effort to prevent RV failure, some authors advocate for the routine use of phosphodiesterase type 5 inhibition, nitric oxide, or Epoprostenol Sodium (Flolan) therapy in every patient with pre-implant PVR above 3.[11]

Gastrointestinal Bleeding

Approximately one forth of VAD patients suffer from gastrointestinal bleeding (GI)[54]; half of the bleeding episodes originate from the upper GI tract. Although angiodysplastic lesions are the predominant cause of bleeding, stress and peptic ulcers are common in this patient population as well.[54]

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The increased risk of bleeding is associated with several factors. First, similar to the Heyde syndrome of aortic stenosis, LVAD rotors generate high shearing forces leading to degradation of von Willebrand factor and acquired von Willebrand syndrome.[55–57] Second, the continuous-flow devices generate low pulse pressures, which may cause GI hypoperfusion leading to formation of angiodysplastic lesions.[58] In addition, most VAD patients are treated regularly with anticoagulation and antiplatelet regimens, which further increases the risk of bleeding.[54] *Figure 3* summarises the recommended treatment strategy of GI bleeding.[59]

Infection and Sepsis

Infection is a major cause for morbidity and mortality in LVAD patients. Although the prevalence of VAD associated infections is improving with second and third generation devices, it continues to be a worrisome complication, with 20 % of VAD deaths attributed to infection.[60,61]

According to the International Society of Heart and Lung Transplantation (ISHLT) data, 87 % of VAD infections are bacterial (primarily Staphylococcus and Pseudomonas species) with the reminder being mostly fungal.[62,63] The clinical presentation of VAD infections may be nonspecific and misleading, with symptoms such as lethargy, fatigue, or anorexia, with or without fever or shock.[64] *Table 7* summarises the ISHLT Infectious Diseases Working Group definition of infection in VAD patients.

Driveline infections are the most prevalent infections in VAD patients and may reflect the presence of a deeper infection of the device hardware (pump, cannula) or the pocket space. Due to the marked variability in the clinical presentation, vigilance is required for an early diagnosis of infection.

The Future of Ventricular Assist Device Therapy

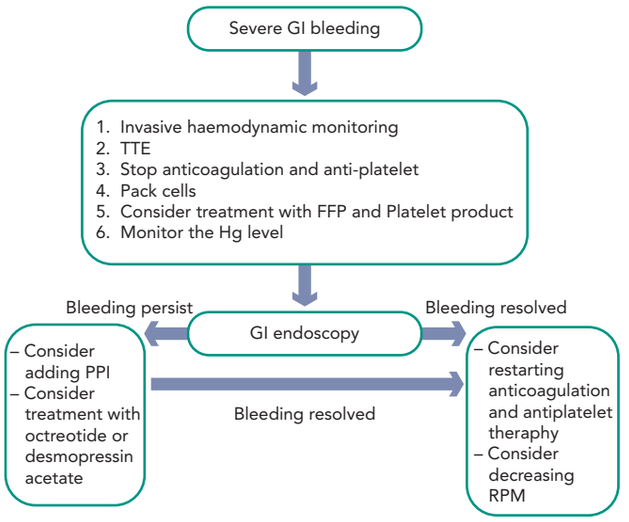
The surge in the prevalence of HF worldwide will result in a substantial rise in the number of patients treated with long-term MCS. The next generation devices are currently being evaluated in clinical trials. These devices are smaller and easier to implant. Moreover, they are designed to have more flexible percutaneous leads, in an effort to decrease the risk of infections.[65,66] Future devices will be more physiologic and will be able to automatically accommodate to the patient's physical activity and position. In addition, devices in the future will have trans-dermal charging so that the system is totally within the body, which will further decrease the risk of infection, and allow patients to swim and shower with no limitation on daily activities.

Table 7: ISHLT Infectious Diseases Working Group definition of infection in VAD patients[64]

VAD-specific infections	Related to the device hardware, occurring only in patients with VAD	• Pump and/or cannula Infections • Pocket Infections • Percutaneous Driveline Infections
VAD-related infections	Occur also in patients who do not have VAD	• Infective endocarditis • Bloodstream infections • Mediastinitis
non-VAD infections	Infections that are unlikely to relate to the VAD therapy.	• Lower respiratory tract infection • Cholecystitis • *Clostridium difficile* • Urinary tract infection

VAD = ventricular assist device. Modified from Hannan MM, et al.[64]

Figure 3: Treatment Strategy of GI Bleeding



GI = Gastrointestinal; TTE = Trans-esophageal echocardiogram; FFP = Fresh frozen plasma; Hg = Haemoglobin; PPI = Proton pump inhibitor. Modified from: Suarez J, et al. [59]

With the accumulating experience and improved outcomes, it is likely that the indications for LVAD implantation will expand and include patients with less severe HF. Finally, there is an ongoing interest in treating HF patients with preserved LVEF with durable MCS.[67]

In conclusion, MCS has emerged as an essential option for advanced HF, with increasing number of patients treated with this modality. These devices significantly improve survival and quality of life in appropriately selected patients. Awareness of the unique complications and clinical presentations is crucial for the long-term management of VAD patients. ■

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