Ventricular Assist Device – How to Obtain Optimal Benefits?

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1. Introduction

Heart failure is now acknowledged to be the most common malignant disease in industrialized countries, with advanced heart failure having a worse prognosis than most forms of cancer (Garg, Yusuf 1993). Advances in pharmacological treatment have helped patients in all stages of systolic dysfunction, even those with NYHA IV symptoms (the Captopril-Digoxin Multicenter Research Group 1988, Packer et al. 1996, the RALES Investigators 1996). The Working Group on Heart Failure of the European Society of Cardiology has promoted a number of initiatives aimed at improving the treatment of heart failure (ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008).

Despite advances in pharmacological treatments aimed at a neurohormonal blockade for heart failure, there is still a growing number of patients with advanced symptoms who suffer significant morbidity and mortality.

Mechanical stresses on the myocardium (increased preload and afterload) and chronic neurohormonal activation conspire to propagate the maladaptive ventricular remodeling responsible for the insidious nature of heart failure. Recent studies suggest that further pharmacological neurohormonal blockade may be neither safe nor effective (Mann 2004). This finding has led to the concept that the limit to which neurohormonal and cytokine mechanisms can be blocked in heart failure patients has already been reached (Cohn, Tognoni 2001). The problem of how to treat patients worldwide who develop advanced heart failure despite optimal medical therapy has not yet been resolved (Gronda, Vitali 1999).

Transplantation provides the most effective therapy for this condition, but the shortage of donor organs results in <10% of potential recipients actually receiving a transplant (Deng et al. 2001). This situation has forced scientists to search for alternative methods of treatment.
At present end-stage chronic heart failure is a significant clinical problem as well as a subject of scientific interest. Transplant candidates whose disease reaches its final stage before an appropriate donor heart becomes available might be considered eligible for temporary or permanent mechanical circulatory support (MCS). This is why ventricular assist devices (VADs) capable of completely supporting the circulation are taking on an increasingly important role in heart failure therapy. The concept of circulatory assistance is not new. The need for such temporary support for hours or days has been recognized for over 60 years and still exists (Norman 1974). It is recognized that device-based approaches, ranging from the use of devices for monitoring patient status in order to anticipate exacerbation of congestive heart failure and preemptively adjust therapy to the application of devices for supporting pre-terminal patients with end-stage disease, will assume an increasingly important role in treating the growing number of patients with advanced heart failure (Kantrowitz et al. 1968). Mechanical circulatory support was first used clinically in 1953 with the implementation of cardiopulmonary bypass (Gibbon 1954). This breakthrough led to numerous surgical treatments for a variety of cardiac disorders. The success of cardiopulmonary bypass stimulated research into other innovative techniques for supporting the circulation. Counterpulsation with the intra-aortic balloon pump (IABP) was first applied clinically in 1967 to support patients with acute heart failure (Kantrowitz et al. 1968). From 1953 congestive heart failure patients were occasionally supported temporarily by cardiopulmonary bypass (Dennis 1966), an implantable ventricular assist device (VAD) (De Bakey et al. 1966) or a totally artificial heart (TAH) (Cooley et al. 1969). Although the overall success rate was limited, this early experience did prove that mechanical circulatory support could adequately sustain a patient’s circulation until cardiac function recovered or a donor heart could be obtained. In the early 1980s the introduction of cyclosporine-based immunosuppression allowed heart transplantation to become a widely accepted therapeutic alternative. During the same decade clinical trials were initiated to evaluate the safety and efficacy of MCS systems in supporting terminally ill transplant candidates until a suitable donor heart could be found. VADs are important bridges to cardiac transplantation. The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial revealed that they could be used as long-term destination therapy for non-transplant candidates (Rose et al., 1999). The use of a wearable ventricular assist device (VAD) in the treatment of advanced heart failure has steadily increased since 1993, when these devices became generally available. Since this time there has been rapid progress in the development of left ventricular assist device technology and artificial hearts.

2. VADs — indications for support

Patients with end-stage heart failure have a poor quality of life, a very high mortality rate, and are potential candidates for implantation of a ventricular assist device (VAD). Although cardiac transplantation (CTX) is associated with high 1- and 10-year survival rates, organ supply is limited. The technical improvements and proven success of implantable VADs have made it a reasonable treatment option in these patients, either as a bridge to cardiac transplantation or as destination therapy – Table 1 (2010 Focused Update of ESC guidelines on device therapy in heart failure).

Mechanical circulatory support is life saving in patients who fail to improve or stabilize with intravenous inotropes or vasodilators, IABP support and mechanical ventilation. Hemodynamic criteria for VAD insertion are as follows (Oz et al., 1995):
- cardiac index < 2 L/min/m²;
- systolic blood pressure < 90 mm Hg;
- pulmonary capillary wedge > 20 mm Hg;
- urine output < 20 mL/h;

when these are found despite pharmacological support, optimal fluid loading and use of IABP as appropriate.

Patient selection for VAD is crucial. Most patients are on continuous inotropic support. Patients with severe renal, pulmonary, or hepatic dysfunction as well as patients with active infection, carcinoma with metastases, significant blood dyscrasias, cerebral vascular disease or cardiogenic shock should not be considered as candidates (Lund et al., 2010).

Each case is assessed individually and criteria are used as a guide only. Some patients have the VAD inserted prior to these criteria being met. In planning the application of the assist device we must decide whether one or both ventricles require support. Insertion of an implantable VAD complicated by early right ventricular failure has a poor prognosis and is largely unpredictable. Patients with risk factors for right ventricle dysfunction (the need for circulatory support, female gender, non-ischemic etiology) may best be treated with a biventricular assist device or a TAH. The next questions arising are whether the VAD should be implanted as a bridge to transplantation or as destination therapy and how long mechanical support will be required. Selection of the appropriate device depends on a number of considerations, including the anticipated duration of patient support, the need for right-side support and the patient’s size. Excluding the strict contraindications to VAD, insertion is very important.

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Patient population</th>
<th>Class of recommendation</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVAD may be considered as destination treatment to reduce mortality</td>
<td>NYHA functional class IIIB/IV LVEF ≤25% Peak VO₂ &lt; 14 mL/kg/min</td>
<td>IIb</td>
<td>B</td>
</tr>
</tbody>
</table>

LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

Table 1. Recommendation in patients with severe heart failure ineligible for transplant (2010 Focused Update of ESC guidelines on device therapy in heart failure).

One recent study was conducted in 200 patients, who were randomized in a 2:1 ratio to a continuous-flow device (HeartMate I) or a pulsatile device (Slaughter et al., 2009) as destination therapy. Patients were in NYHA function class IIIB/IV with an LVEF of ≤25%. A peak VO₂ of ≤14 mL/kg/min was an inclusion criterion in HEART MATE II but gas-exchange data during exercise are not routinely available in clinical practice and may be inconclusive. The primary composite endpoint was, at 2 years, freedom from disabling stroke or reoperation to repair or replace the device. Secondary endpoints included actuarial survival. The mean age of the patients was 64 years, and the mean left ventricular ejection fraction was 17%. The primary endpoint was achieved in more patients with the continuous-flow device (46 vs. 11%, P < 0.001) and actuarial survival at 2 years was higher (58 vs. 24%, P = 0.008). Another study examined 281 patients in whom
the continuous device was implanted as a bridge to cardiac transplantation (Pagani et al., 2009). After 18 months, 222 patients (79%) underwent cardiac transplantation, left ventricular assist device removal for cardiac recovery, or required ongoing LVAD support (Drews et al., 2010). The INTERMACS registry, an National Institutes of Health (NIH)-supported initiative, demonstrates that in practice ~10% of patients receiving an LVAD are not considered candidates for CTX at the time of implantation (Kirklin et al., 2010).

3. Patient selection and preoperative considerations

The highest risk of death after ventricular assist device implantation is before hospital discharge. Thus, patient selection and the timing of implantation are two of the major determinants of success. Main selection criteria include assessment of the patient’s severity of illness and ability to successfully undergo the implant procedure. Preoperative selection criteria which predict successful outcome are difficult to evaluate. The selection of appropriate candidates with a potentially good outcome is of major importance in VAD implantation.

Patients are assessed for appropriateness for LVAD support based on the degree of illness, ability to successfully undergo the operative procedure and ability to be discharged home with adequate family/caregiver support for long-term success. Mortality rates are high after implantation of a ventricular assist device, occurring mainly in the early phase post-implant during the time in the intensive care unit.

4. Patient assessment before LVAD support

The Heart Failure Survival Score (Aaronson et al., 1997) and the Seattle Heart Failure Model (Levy et al., 2006) estimate a heart failure patient’s expected survival during the next 1 to 2 years on medical management and identify patients at high risk of death who might benefit from LVAD support.

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) registry, which follows all long-term mechanical circulatory support systems in the United States, has defined patient profiles that can help identify risks associated with the timing of implantation (Holman et al., 2009; Stevenson et al., 2009) – Table 2. The current 6-month survival data for patients receiving pulsatile LVADs indicate that patients in profile 1, cardiogenic shock, have the lowest survival, and those in profile 3, stable on inotropes, have the best survival (Kirklin et al., 2010).

These data indicate that patients with cardiogenic shock may be too sick for permanent LVAD support. Thus, for these patients, consideration should be given to immediate stabilization with biventricular support, using temporary percutaneous or surgically placed systems or other appropriate treatments, to optimize their condition before implant surgery. This is especially true for the destination therapy indication because most patients can be stabilized and their risks assessed and reduced before implantation. Implantation of a long-term LVAD should not be considered for patients with irreversible major end-organ failure, uncertain neurological status, severe hemodynamic instability, major coagulopathy, prolonged need for mechanical ventilation, sepsis, or right-heart failure (Slaughter et al. 2010).
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<table>
<thead>
<tr>
<th>Profile</th>
<th>Description</th>
<th>Time to MCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>“Crashing and burning”—critical cardiogenic shock</td>
<td>Within hours</td>
</tr>
<tr>
<td>2</td>
<td>“Progressive decline”—inotrope dependence with continuing deterioration.</td>
<td>Within a few days</td>
</tr>
<tr>
<td>3</td>
<td>“Stable but inotrope dependent”—describes clinical stability on mild-to-moderate doses of intravenous inotropes (patients stable on temporary circulatory support without inotropes are within this profile).</td>
<td>Within a few weeks</td>
</tr>
<tr>
<td>4</td>
<td>“Recurrent advanced heart failure”—“recurrent” rather than “refractory” decomposition</td>
<td>Within weeks to months</td>
</tr>
<tr>
<td>5</td>
<td>“Exertion intolerant”—describes patients who are comfortable at rest but are exercise intolerant.</td>
<td>Variable</td>
</tr>
<tr>
<td>6</td>
<td>“Exertion limited”—describes a patient who is able to do some mild activity but fatigue results within a few minutes of any meaningful physical exertion.</td>
<td>Variable</td>
</tr>
<tr>
<td>7</td>
<td>“Advanced NYHA III”—describes patients who are clinically stable with a reasonable level of comfortable activity, despite a history of previous decompensation that is not recent.</td>
<td>Not a candidate for MCS</td>
</tr>
</tbody>
</table>

INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; MCS, mechanical circulatory support; NYHA, New York Heart Association.

Table 2. INTERMACS Patient Profiles and Timeframe for Initiating Mechanical Circulatory Support (Holman et al., 2009; Slaughter et al. 2010).

5. Risk factors for operative mortality

Lietz and Miller (Lietz et al., 2007) analyzed preoperative clinical data from 222 patients who received the HeartMate XVE LVAD for destination therapy. They established a risk scoring system to estimate survival after implantation. The multivariate analysis produced 9 risk factors for 90-day mortality, which were assigned a weighted score (Table 3). The cumulative scores for each patient were then used to determine the risk category: 0 to 8, low risk; 9 to 16, medium risk; 17 to 19, high risk; and >19 very high risk. The survival to hospital discharge was 87.5%, 70.5%, 26%, and 13.7% for the low-, medium-, high-, and very high-risk groups, respectively.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Score</th>
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<tbody>
<tr>
<td>Platelet count &lt; 148 x 10^3/µL</td>
<td>7</td>
</tr>
<tr>
<td>Serum albumin &lt; 3.3 g/dL</td>
<td>5</td>
</tr>
<tr>
<td>International normalization ratio &gt; 1.1</td>
<td>4</td>
</tr>
<tr>
<td>Vasodilator therapy</td>
<td>4</td>
</tr>
<tr>
<td>Mean pulmonary artery pressures &lt; 25 mm Hg</td>
<td>3</td>
</tr>
<tr>
<td>Aspartate aminotransferase &gt; 45 U/mL</td>
<td>2</td>
</tr>
<tr>
<td>Hematocrit &lt; 34%</td>
<td>2</td>
</tr>
<tr>
<td>Blood urea nitrogen &gt; 51 mg/dL</td>
<td>2</td>
</tr>
<tr>
<td>No intravenous inotropes</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 3. Risk Factors for 90-Day Mortality and the Weighted Scores (Lietz et al., 2007)
In 1995, Oz et al. found 7 preoperative factors that predicted poor outcome in a group of 56 patients. These consisted of urine output <30 mL/h, central venous pressure >16 mm Hg, mechanical ventilation, prothrombin time (PT) >16 seconds, re-operation, leukocyte count >15,000/mm$^3$ and temperature >101.5°F. However, they used only a first-generation device and prediction of urine output <30 mL/h takes at least 1 hour (Oz et al. 1995).

Therefore, this score was revised by Rao et al. based on 130 patients and more easily obtained and quickly accessible parameters (ventilation, post-cardiotomy, pre-VAD, CVP >16 mm Hg, prothrombin time > 16 seconds) (Rao et al. 2003). In 2001, Deng et al. reviewed the Novacor registry data in 464 patients and highlighted 5 parameters – respiratory failure with septicemia, preexisting right heart failure, age >65 years, acute post-cardiotomy, and acute infarction – predicting mortality during VAD support (Deng et al., 2001). In 2004, Chen et al. showed that lactate, and lung and kidney injury are predictive of poor outcome among patients on extracorporeal membrane oxygenation (ECMO) support that was switched to VAD support (Chen et al., 2004). In addition, some studies showed that predictors of poor outcome were similar in total artificial heart or biventricular VAD implantation as compared with VAD implantation. Scientists also tried to use existing intensive care scores, such as the APACHE II score, to predict VAD mortality (Gracin et al., 1998). However, these already existing scores, which attempt to predict mortality after VAD implantation, are based on first-generation pulsatile devices and not on modern second- or third-generation devices, and they assess overall death after VAD as the primary outcome. They do not specifically focus on mortality in the intensive care unit, which is especially dependent on preoperative clinical status. Klotz et al. implemented a pre-operative risk score to predict mortality in the intensive care unit after VAD implantation by using easily obtained and quickly accessible clinical parameters (Klotz et al., 2010).

By focusing on mortality in the intensive care unit, they tried to evaluate preoperative patients who were too sick for mechanical support and may not have survived their stay in the ICU. In 241 VAD patients, 100 preoperative markers were related to mortality in the ICU using univariate analysis and ROC curves, followed by multinomial logistic regression analyses. The mortality rate in the ICU was 32.0%.

The parameters with the highest negative impact on survival in the ICU were: age>50 years, ischemic cardiomyopathy, re-do surgery, on ECMO, on IABP, previous cardiac surgery, ventilation, emergency implant, inotropic support, renal replacement therapy, preoperative resuscitation, transfusion, blood urea nitrogen >40 mg/L, creatinine>1.5 mg/dL, lactate >3 mg/dL, platelets <100 x 1000/µL, whole blood cell count >13,000/µL, C-reactive protein > 8 mg/dL, hemoglobin <12 g/dL, hematocrit <35%, lactate dehydrogenase >500 U/liter, creatinine kinase>200 U/liter, troponin >20 ng/mL.

The risk for mortality in the intensive care unit was as follows: low <15 points, medium 16-30 points, high >30 points.

This score distinguishes clearly between the different urgencies of VAD implatation – Figure 1.

These observations suggest that in-hospital mortality can be predicted preoperatively with easily obtained and quickly accessible parameters. Patients who initially present as high-risk or very high-risk are most likely to benefit from a period of optimization therapy to attempt to lower their risk score (for example: coagulation, nutrition, renal function, right atrial pressure) and then become more suitable candidates for LVAD support. Patients with a low risk should be considered for prompt elective LVAD implantation before their condition worsens.
Fig. 1. Mortality in the ICU, depending on VAD implant urgency. Post-cardiotomy is defined as patients with unsuccessful weaning from bypass and on ECMO support.

Pre-implant optimization of comorbid conditions is very important in minimizing the incidence and severity of postoperative adverse events and for enhancing survival. The most influential pre-implant measures are:

- **Improving nutritional status**

  Malnutrition is very common in patients with advanced heart failure. If not improved, it increases the risk of infection, decreases the body’s ability to recover after surgery, and is generally associated with poor outcomes. Studies have shown that cachexia (BMI <22 kg/m²) is associated with a high risk for peri-operative death, often due to infection (Manop et al., 2009; Holdy et al., 2005).

  Markers of severe malnutrition include a BMI <20 kg/m², albumin <3.2 mg/dL, pre-albumin <15 mg/dL, total cholesterol <130 mg/dL, lymphocyte count <100, and purified protein derivative skin test anergy. The nutrition needs to be improved before LVAD implantation (a pre-albumin level >15 mg/dL). For patients with pre-albumin <15 mg/dL, enteral feedings are often helpful preoperatively and should be continued after implantation until the patient is taking adequate nutrition.

  It is equally important to maintain adequate nutrition after the implant surgery. Data from Lockard et al. have shown that patients with a pre-albumin level of <15 mg/dL at 2 weeks after LVAD implantation had a significantly greater risk of dying in the hospital (Lockard et al., 2009).

- **Lowering pulmonary vascular resistance to optimize right-heart function and to reduce right atrial pressure and secondary hepatic congestion**

  Left ventricular unloading with a LVAD should decrease right ventricular after-load by reducing pulmonary artery pressures (PAPs) (Farrar et al. 1985).

  However, mechanical support may increase systemic venous return to a myopathic right heart that is unable to accommodate the additional volume. Furthermore, reduction in left ventricle pressure can cause the interventricular septum to shift leftward, potentially causing disadvantageous geometric changes in the right ventricle that reduce the septal contribution to right ventricle stroke volume and exacerbate tricuspid regurgitation (Farrar...
et al. 1985). Importantly, right ventricle failure after implantation can be anticipated preoperatively and improved with various therapies that optimize its function. An analysis of 484 patients in the HeartMate II Bridge to Transplant clinical trial demonstrated the following independent predictors of right ventricle failure: preoperative ventilatory support, central venous pressure (CVP)/pulmonary capillary wedge pressure ratio >0.63, and blood urea nitrogen >39 mg/dL (Kormos et al., 2010).

Univariate predictors also included a right ventricular stroke work index (RVSWI) <300 mm Hg × mL/m², central venous pressure (CVP) >15 mm Hg, elevated blood urea nitrogen (BUN), and elevated white blood cell count. The HeartMate II trial found no difference in the incidence of right ventricular failure in heart failure patients with non-ischemic vs ischemic etiology.

Other signs of poor right ventricle function can be found with pre-implant echocardiography. Close attention should be paid to RV size, with particular caution extended to patients who have a dilated, poorly contracting right ventricle. Severe tricuspid regurgitation also can be associated with early postoperative RV failure. Some have advocated repair of the tricuspid regurgitation at the time of LVAD implantation if its severity is judged to be more than moderate, either preoperatively or intraoperatively by echocardiogram.

Patients at risk for postoperative right ventricle failure should not necessarily be eliminated from LVAD support. However, the implanting team should promptly treat RV failure using pharmacotherapeutics and mechanical RV support, as appropriate or needed (Slaughter et al. 2010).

- **Aggressively managing volume to minimize right ventricular workload and hepatic congestion**

  A pulmonary artery catheter 24 hours before implantation is useful in most patients to assess the cardiac index and volume status as well as to guide diuretic, vasodilator, and inotropic support. One of the main objectives is to reduce the central venous pressure (CVP) to 15 mm Hg or less. This will aid in reducing the right ventricle workload and minimizing hepatic congestion and the possible need for a right ventricular assist device (RVAD). When the CVP exceeds 20 mm Hg, ultrafiltration and inotrope and vasodilator therapy should be used; also consider temporary RVAD support. Increasing the cardiac index with vasodilators, inotropes, and using an IABP will improve conditions for all organ systems. Medications that can lower pulmonary vascular resistance (PVR) and improve the cardiac index before surgery may be beneficial in reducing the incidence of right ventricular failure after implantation (Galie et al., 2005; Klodell et al., 2007).

Medications that have been shown to reduce PVR include angiotensin-converting enzyme (ACE) inhibitors, hydralazine, nitroglycerin, nitroprusside, nitric oxide, sildenafil, prostaglandins, and inotropes (milrinone and dobutamine).

- **Optimizing coagulation**

  Preoperative abnormal coagulation is common in heart failure patients due to hepatic dysfunction and the use of anticoagulant or antiplatelet medications. When possible, these medications should be stopped before implantation. Vitamin K may be given to reverse the effects of warfarin. For patients who are at high risk of preoperative thrombosis, a continuous infusion of heparin should be given. Because the continuous-flow left ventricular assist device requires systemic anticoagulation, its use in patients with a history of gastrointestinal (GI) bleeding should be carefully considered. Active GI blood loss should
be assessed for 3 to 4 weeks before left ventricular assist device implantation (Slaughter et al. 2010).

- **Optimizing renal, hepatic, pulmonary and neurological function**

Renal dysfunction is a predictor of adverse outcomes in LVAD-supported patients (Sandner et al., 2009; Ma et al., 2008; Butler at al. 2006). Patients in the HeartMate II Bridge to Transplant trial were excluded if their creatinine level was <3.5 mg/dL or if they needed chronic dialysis; 11% of patients had some degree of renal dysfunction after implantation (Miller et al., 2007).

Optimizing renal function preoperatively entails measures to increase renal perfusion and reduce central venous pressure. Renal dysfunction generally improves after LVAD implantation if decreased glomerular filtration rate is due to low cardiac output before implantation.

Liver dysfunction is associated with greater need for intraoperative and perioperative blood transfusion, which can result in worsened right-heart function and the need for RVAD support. Many centers screen patients with clinical evidence of significant right heart failure or serological evidence of hepatic dysfunction using hepatic ultrasound imaging or liver biopsy to rule out cirrhosis.

As with renal function, there is evidence that hepatic function improves after implantation of a continuous-flow LVAD (Radovancevic et al., 2007; Letsou et al., 2003). Specific management strategies should be initiated to improve hepatic function before an LVAD is implanted in individuals with abnormal values for prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR). Right heart pressure and pulmonary vascular resistance should be decreased using combinations of drugs to reduce pre-load and after-load, ultrafiltration, or both.

Patients with severe obstructive or restrictive pulmonary disease are not eligible for LVAD therapy. When pulmonary function testing can be performed reliably, and the forced vital capacity, forced expiratory volume at 1 second, and carbon monoxide diffusing capacity are all less than 50%, exclusion from LVAD implantation should be considered.

Patients with neurological or psychiatric disease that compromises their ability to use and care for external system components, or to ambulate and exercise, are not appropriate candidates for LVAD support (Tylus-Earl et al. 2009).

Psychiatric disorders, drug abuse, and other psychosocial issues must be investigated to assess the patient’s ability to understand and comply with care instructions. All patients with an audible bruit or peripheral arterial disease, diabetes, or age >60 years, should undergo a carotid ultrasound study to rule out significant stenosis or the presence of unstable plaque. Patients with previous stroke also warrant computed tomography (CT) scan or magnetic resonance imaging (MRI) to establish a preoperative baseline study. Patients must have a reliable means of transportation for follow-up visits and a convenient, reliable telephone service to call for medical help in an emergency.

- **Treating any infection or providing prophylactic antibiotic therapy**

Patients with active systemic infection should not be considered for LVAD support because infection is one of the leading causes of morbidity and death. Implantation should be delayed for patients with localized infections that can be effectively treated, if clinically feasible.

We should try to cope with patients with established or suspected infections, prolonged intubation, cutaneous lesions at surgical sites, or other comorbidities, including multisystem
organ dysfunction, immunosuppression, poorly controlled diabetes, renal failure, malnutrition, or debilitation (Slaughter et al. 2010).

6. Device selection

Mechanical support can be applied short-term in an individual patient as a bridge to transplantation or can be applied long-term as in destination therapy. For example, if a patient with myocardial infarction and cardiogenic shock experiences a cardiac arrest that requires prolonged resuscitation, the heart failure specialist would know that percutaneous mechanical support could precede a potential LVAD until the neurological status is determined. If an LVAD is subsequently implanted, the patient’s candidacy for transplantation versus discharge and long-term LVAD maintenance therapy (i.e., destination therapy) must be considered.

Numerous devices are now approved by the Food and Drug Administration (FDA) for therapy in acute heart failure and in chronic decompensated congestive heart failure – Table 4.

<table>
<thead>
<tr>
<th>Company</th>
<th>Device</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abiomed, Inc</td>
<td>Abiocor Total Artificial Heart</td>
<td>Total artificial heart</td>
</tr>
<tr>
<td>SynCardia Systems, Inc</td>
<td>SynCardia CardioWest</td>
<td>Total artificial heart</td>
</tr>
<tr>
<td>Thoratec Corp</td>
<td>HeartMate II Left Ventricular Assist Support</td>
<td>Left ventricle</td>
</tr>
<tr>
<td></td>
<td>HeartMate Implantable Pneumatic HeartMate Vented Electric HeartMate Extended Vented Electric Thoratec Implantable Ventricular Assist Device Thoratec Paracorporeal Ventricular Assist Device</td>
<td>Left ventricle Left ventricle Left ventricle Left ventricle Left or right ventricle Left or right ventricle</td>
</tr>
<tr>
<td>WorldHeart, Inc</td>
<td>Novacor PC</td>
<td>Left ventricle</td>
</tr>
</tbody>
</table>

Table 4. Food and Drug Administration-Approved Durable Devices (Potential for Patient Discharge)

These devices can be divided according to site of placement (commonly extra-, para- or intracorporeal) and type of flow generator system (centrifugal, axial or diaphragm). Intracorporeal ventricular assist device are presented in Figure 2.

Device selection depends not only on specific patient characteristics and the pathology of the patient’s heart failure but also on device characteristics, device availability and the experience of the surgical team (D’Alessandro et al. 2002, Goldstein et al. 1998).

Patients in profound cardiogenic shock require support to avoid permanent end-organ dysfunction and increase their chances of survival. The preferred devices are the ABIOMED BVS 5000 or Thoratec device. These devices may provide full biventricular support, re-establishing near normal hemodynamics while myocardial recovery is awaited. If prolonged
Fig. 2. Intracorporeal ventricular assist devices.
support is expected, conversion to a longer-term device such as an implantable LVAD or TAH should be considered. The Thoratec device has the advantage of providing long-term, extracorporeal support. Device selection for long-term support is much more complicated and is often subjective and based on the surgeon’s experience. For smaller patients (body surface area < 1.5 m²) the Thoratec device and perhaps a continuous-flow pump are the only options (Delgado et al. 2002).

7. Continuous versus pulsatile-flow pumps

Long-term implantable mechanical circulatory assistance as a clinically viable entity started with the approval of the HeartMate XVE as a bridge to transplantation. Results of the REMACH trial led to the device being approved for destination therapy (Lietz et al., 2007). The other implantable pulsatile devices approved in the United States are the WorldHeart Novacor left ventricular assist device and SynCardia total artificial heart. These first-generation pumps were designed to mimic nature and produce pulsatile blood flow. There has been much debate over the need for pulsatility. Animal data suggest that non-pulsatile flow might not deliver as much perfusion to the distal vasculature and might lead to weakening of the muscle in the walls of major arteries (Yada et al., 1999; Potapov et al., 2000).

The pulsatile devices are bulky as they have to at least be the size of the bladder displacement (usually 60 to 80 cc) and hence have to be placed in the pre- or intraperitoneal space. A diaphragm or sac is required to eject the blood and flexing of this biomaterial interface can lead to failure after millions of cycles. Mechanical energy is derived from a pusher plate-type motor, which has decreased device resistance. These technical limitations mandated by pulsatile devices have led to decreased reliability and durability and a high incidence of infections. Furthermore, the major surgery required for implantation increases the rate of bleeding, perioperative complications, length of hospital stay and need for rehabilitation.

The next generation of devices consists of continuous-flow pumps. The HeartMate II device is approved as a bridge to transplant and destination therapy. The HeartWare HVAD, Jarvik 2000, Trumo DuraHeart and Ventracor VentrAssist devices are in clinical trials. The Cleveland Clinic TAH (Fumoto et al. 2010; Fukamachi et al. 2010) can transition continuous flow principles to a TAH and allow the technology to be used in patients requiring biventricular support. Compared with previous pulsatile devices, continuous-flow pumps cannot completely decompress the left ventricle as the native heart must have some residual volume to prevent suction events. Therefore, the native heart continues to eject and this provides a moderate amount of pulsatility. This low level of pulsatility is apparently enough to increase end-organ perfusion and allow these patients to recover from chronic congestive heart failure. In many patients, this ejection occurs through the left ventricular assist device and the aortic valve can remain closed. They contain only one moving part, the rotor, which is why they tend to be much more reliable. Continuous-flow LVADs are also silent during operation and create minimal motion and vibration. These features make continuous-flow devices more suitable for use in patients with smaller body size. Because they are much smaller and do not have the constant motion caused by blood displacement, the infection rates have dramatically decreased (Miller et al. 2007; Bielecka et al., 2007).

The trend in circulatory assistance is toward continuous-flow devices. They offer many advantages over the pulsatile devices in terms of size, reliability, durability and infection.
However, long-term results will need to be followed closely, specifically with regard to the perioperative period and the incidence of cerebrovascular accident despite appropriate anticoagulation (Jeevanandam 2010; Boyle 2009).

Table 5 provides a general comparison of the 2 types of LVADs in clinical use.

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Pulsatile-flow VAD</th>
<th>Continuous-flow VAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of pump</td>
<td>Sac or diaphragm</td>
<td>Centrifugal or axial flow by rotating impeller</td>
</tr>
<tr>
<td>Main hemodynamic characteristics</td>
<td>Intermittent unloading of ventricle; pulsatile arterial pressure; asynchronous with heart</td>
<td>Continuous unloading of ventricle</td>
</tr>
<tr>
<td>Physiological flow variables</td>
<td>Pre-load dependant</td>
<td>Pre-load and after-load dependant</td>
</tr>
<tr>
<td>Mechanical flow variables</td>
<td>Automatic or fixed rate and stroke volume capacity</td>
<td>Set speed of the impeller rotation</td>
</tr>
<tr>
<td>Size</td>
<td>Large, intracorporeal devices limited to large patients, extracorporeal devices especially suited for smaller patients or for biventricular support</td>
<td>Smaller, accommodates most patients, excluding infants</td>
</tr>
<tr>
<td>Blood flow capacity</td>
<td>Up to 10 liters/min</td>
<td>Up to 10 liters/min</td>
</tr>
</tbody>
</table>

Table 5. Comparison of pulsatile and continuous-flow ventricular assist devices (Slaughter et al. 2010).

8. Axial and centrifugal pumps

Continuous-flow ventricular assist devices use axial-flow or centrifugal-flow blood pumps. The most modern axial flow devices offer significant potential advantages over earlier devices, because they are smaller, simpler and less obtrusive to the patient, yielding a better quality of life. The blood flow is essentially non-pulsatile and pump output is dependent mainly on afterload. In addition, because of their smaller size, they can be used in smaller patients, including children (Frazier et al. 2005). The axial flow pumps in current use are: the MicroMed/DeBakey VAD (MM-D VAD) and the Jarvik 2000 Heart, which have certain similarities in design and function. The Jarvik 2000 Heart, in particular, has many advantages. Its implantation can be performed without median sternotomy, which makes the eventual transplantation operation easier. There is no inflow cannula, which rids the patient of the thrombotic and hemolytic problems encountered with inflow cannulae. Circulation to the coronaries, the brachiocephalic, the left carotid and the subclavian arteries is thus provided by retrograde flow. There is no need for an external pocket in the mediastinum or the peri-peritoneum, which decreases the risk of infection (Westaby et al. 2000). The MicroMed/DeBakey VAD consists of a titanium inflow cannula that is inserted into the left ventricular apex and leads to the pump proper, which connects to the ascending aorta via a vascular graft. The pump is implanted through a median sternotomy in a small extracardiac pocket (Noon et al. 2000).
The HeartMate II device is an axial flow pump that has a spinning rotor as its only moving part and the direction of blood is parallel to the rotor. The HeartMate II has a left ventricular apical inflow cannula with a sintered titanium blood-containing surface. No compliance chamber or valves are necessary. The outflow cannula is connected to a Dacron graft, which is then anastomosed to the ascending aorta in a similar fashion to that achieved with the original HeartMate XVE. The pump is designed to deliver as much as 10 L/min of cardiac output and is placed either intraperitoneally or extraperitoneally (Delgado et al. 2005; Noon et al., 1999).

The HeartMate II LVAD is shown in Figure 2.

![Fig. 3. The HeartMate II LVAD.](image)

HeartMate II has FDA approvals as bridge-to-transplant and destination therapy. Two other axial-flow pumps are: Incor (left ventricular assist device with magnetic bearing) and Synergy (left ventricular assist device with blood-immersed bearings). Centrifugal pumps use the pump mechanism of a standard heart bypass. In devices such as the HVAD, DuraHeart, Levacor VAD and EVAHEART LVAS the inflow and outflow of blood are in perpendicular directions (Bielecka et al. 2007).

New centrifugal systems include the bearingless system. This drive system is magnetically coupled to an external power source and pump flow is related to rotation speed. The advantages of the centrifugal pump are simplicity of design, versatility and the relatively low costs of manufacture and operation. It can be used as a femoral-femoral bypass or as a left (right) ventricular-to-aortic (pulmonary artery) bypass. Its main disadvantages are the need for heparinization, difficulty in chest closure, the need for intensive monitoring and the inability to generate a pulsatile flow. The pump is used primarily as a bridge to recovery in cardiogenic shock. The total duration of support with a centrifugal pump is usually limited to no more than two to three weeks (Noon et al. 1999).

The Interagency Registry For Mechanical Circulatory Support (INTERMACS) report examined the changing patterns of practice in the application of device type (continuous-flow vs pulsatile) and device strategies during the past 3 years (Kirklin et al., 2010). The INTERMACS playing field changed dramatically in April 2008 when the HeartMate II axial flow pump (Thoratec) received FDA approval for clinical use as bridge-to-transplant
therapy in the United States. When continuous flow technology is routinely available for long-term destination therapy, and as multiple continuous-flow pumps are approved, INTERMACS offers a unique opportunity to compare and contrast these technologies in the setting of evolving indications, changing patient profiles, and refinement of device strategy in the developing landscape of mechanical circulatory support.

This report focuses on the 1,092 patients who received primary left ventricular assist device implants among the total of 1,420 patients who received primary and secondary devices. The distribution of pre-implant device strategies continues to focus on bridging patients to cardiac transplantation with the device as a bridge to candidacy or bridge to transplant. The initial strategy was permanent in nearly 10% – Table 6.

<table>
<thead>
<tr>
<th>Pre-implant device strategy</th>
<th>No. (N=1092)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bridge to transplant</td>
<td>496</td>
<td>45.4</td>
</tr>
<tr>
<td>Bridge to candidacy</td>
<td>458</td>
<td>41.9</td>
</tr>
<tr>
<td>Planned destination therapy</td>
<td>100</td>
<td>9.2</td>
</tr>
<tr>
<td>Bridge to recovery</td>
<td>25</td>
<td>2.3</td>
</tr>
<tr>
<td>Rescue therapy</td>
<td>10</td>
<td>0.9</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>0.3</td>
</tr>
<tr>
<td>Total</td>
<td>1092</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Table 6. Device strategy at Time of Implant of Primary LVAD (INTERMACS) (Kirklin et al., 2010).

According to INTERMACS data risk factors reflecting older age, greater severity of right ventricular failure and cardiogenic shock at implant predict a higher likelihood of early death among all LVAD patients. The use of a pulsatile pump was a risk factor for death in the constant phase. Because continuous-flow pumps have only accrued a mean follow-up of 4.6 months, adverse events among pulsatile vs continuous-flow pumps during the first 6 months after implantation were assessed. Generally, the events per 100 patient-months are importantly reduced in patients with continuous-flow devices versus pulsatile pumps for device malfunction, infection, hepatic dysfunction, and neurological events – Table 7.

INTERMACS has analyzed the first 1000-plus patients with primary implantation of LVADs during a transitional period from pulsatile technology to continuous-flow pumps. The shift toward implantation of axial flow technology since its approval by the Food and Drug Administration is dramatic. This trend has been accompanied by continued fluctuation in the designation of the primary device strategy as bridge to transplant, bridge to candidacy and destination therapy (Kirklin et al., 2010).

The use of mechanical device support in the congenital heart disease patient requires knowledge of anatomical and physiological factors such as body size, residual intracardiac shunts, the presence of a single ventricle, or venous anomalies and/or arterial anomalies that may impact the success of device implantation, and the effectiveness of the VAD support.

Evidence-based clinical management of LVAD-supported patients is becoming increasingly important for optimizing outcomes. Patient and device selection, preoperative preparation and the timing of LVAD implantation are some of the most important elements critical to successful circulatory support and are principles universal to all devices.
Ventricular Assist Devices

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Pulsatile (n = 406)</th>
<th>Continuous (n = 548)</th>
<th>Pulsatile / continuous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device malfunction</td>
<td>45 2.95</td>
<td>17 0.82</td>
<td>3.60 &lt;0.0001</td>
</tr>
<tr>
<td>Bleeding</td>
<td>369 24.22</td>
<td>360 17.41</td>
<td>1.39 &lt;0.0001</td>
</tr>
<tr>
<td>Cardiac/vascular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right heart failure</td>
<td>48 3.15</td>
<td>46 2.23</td>
<td>1.41 0.05</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2 0.13</td>
<td>2 0.10</td>
<td>1.30 0.37</td>
</tr>
<tr>
<td>Cardiac arrhythmia</td>
<td>154 10.11</td>
<td>218 10.54</td>
<td>0.96 0.65</td>
</tr>
<tr>
<td>Pericardial drainage</td>
<td>44 2.89</td>
<td>30 1.45</td>
<td>1.99 0.003</td>
</tr>
<tr>
<td>Hypertension¹</td>
<td>75 4.92</td>
<td>17 0.82</td>
<td>6.00 &lt;0.0001</td>
</tr>
<tr>
<td>Arterial non-CNS thrombosis</td>
<td>7 0.46</td>
<td>6 0.29</td>
<td>1.59 0.21</td>
</tr>
<tr>
<td>Venous thrombotic event</td>
<td>38 2.49</td>
<td>32 1.55</td>
<td>1.61 0.03</td>
</tr>
<tr>
<td>Hemolysis</td>
<td>11 0.72</td>
<td>12 0.58</td>
<td>1.24 0.29</td>
</tr>
<tr>
<td>Infection</td>
<td>431 28.29</td>
<td>244 11.80</td>
<td>2.40 &lt;0.0001</td>
</tr>
<tr>
<td>Neurological dysfunction</td>
<td>66 4.33</td>
<td>40 1.93</td>
<td>2.24 &lt;0.0001</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>63 4.14</td>
<td>45 2.18</td>
<td>1.90 0.0007</td>
</tr>
<tr>
<td>Hepatic dysfunction</td>
<td>24 1.58</td>
<td>14 0.68</td>
<td>2.32 0.009</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>121 7.94</td>
<td>89 4.31</td>
<td>1.84 &lt;0.0001</td>
</tr>
<tr>
<td>Wound dehiscence</td>
<td>8 0.53</td>
<td>9 0.44</td>
<td>1.20 0.34</td>
</tr>
<tr>
<td>Psychiatric episode</td>
<td>43 2.82</td>
<td>38 1.84</td>
<td>1.53 0.03</td>
</tr>
<tr>
<td>Total burden</td>
<td>1549 101.69</td>
<td>1219 58.96</td>
<td>1.72 &lt;0.0001</td>
</tr>
</tbody>
</table>

¹ - with current reporting, identification of hypertension with continuous-flow pumps is unreliable.
CNS - central nervous system

Table 7. Adverse event rates (events/100 patient months) in the first 12 months post-implant for primary LVADs (INTERMACS) (Kirklin et al., 2010).

9. Intraoperative considerations

Moderate to severe aortic insufficiency and mitral stenosis must be corrected during LVAD implantation.
Inflow cannulas must be directed posteriorly toward the mitral valve. Obstruction may result if the cannula is directed or angled toward the septum or free wall or due to changes in position as the left ventricular chamber size is reduced over time.
Proper placement of the percutaneous lead is important for long-term prevention of infection and damage to wires. Tunnel the percutaneous lead to maximize the amount of velour that is inside the body. It may be positioned in a gentle loop or arc, leaving some internal slack for accidental tugs in the perioperative period.
Certain LVAD implant steps can be taken before initiation of cardiopulmonary bypass (CPB) to minimize CPB time: tunnel the percutaneous lead and anastomosis of the outflow graft to the ascending aorta.
Before the patient is taken off CPB, air removal should be conducted at low LVAD speeds. The patient should be weaned off cardiopulmonary bypass or at minimal CPB support (approximately ≤1 liter/min) before increasing revolutions per minute speeds to permit
complete filling of the left ventricle (>10 mm Hg) and to prevent aspiration of air around the inflow conduit. The pump should be initiated at low speeds and increases made slowly.

If right ventricle dysfunction occurs, resulting in poor LVAD inflow, temporary right-heart bypass can be used to provide blood flow to the LVAD while transitioning from CPB. For more profound right ventricle failure, a temporary RVAD should be considered and implemented expeditiously. Intraoperative echocardiography is essential for identifying valvular pathology, intracardiac thrombi, and an atrial septal defect or patent foramen ovale (PFO). A PFO should be closed at the time of implantation. Intracardiac thrombus identified in the left atria or ventricle should be removed before LVAD implantation. Echocardiography is critical for assessing left ventricle chamber size, cannula position, septal shifting, and aortic valve opening—factors used to determine optimal pump position and speed setting (Slaughter et al. 2010).

10. Postoperative patient and device management

A patient’s right ventricular function can be affected by pump speed. Avoid setting the pump speed so high that it causes a significant leftward septal shift and abnormal right ventricle geometry, which can adversely affect RV function. High pump speeds can also collapse the left ventricle and obstruct flow through the LVAD inlet cannula draining the left ventricle.

Anticoagulation therapy is required during support with continuous-flow LVADs to avoid thrombotic complications. However, results from the HeartMate II Bridge to Transplant trial indicate that anticoagulation requirements for this therapy are less than was initially believed. The results from the clinical trial revealed that the incidence of thrombotic events is very low—much lower than bleeding—which remains one of the most frequent adverse events (Miller et al. 2007; Pagani et al. 2009).

Routine use of heparin is not indicated immediately after the LVAD is implanted. However, there are some clinical conditions of higher thrombotic risk where postoperative heparin may be indicated in the transition to warfarin therapy, such as small patients who have low LVAD flow rates, a small ventricle, previous stroke or transient ischemic attack, chronic atrial fibrillation, or documented left atrial or left ventricle thrombus. Adequate hemostasis should be achieved before anticoagulation is initiated. Patients are usually anticoagulated with warfarin and antiplatelet agents (aspirin) when they are able to take oral medications. Current recommendations are to adjust the warfarin dose to achieve a target INR of 1.5 to 2.5. In addition to warfarin, patients should also be given antiplatelet therapy, such as aspirin (81 to 325 mg daily). If LVAD flow remains low (<3.0 liters/min), consider increasing anticoagulation. If there is a risk of bleeding, decreasing the warfarin dose and increasing or maintaining antiplatelet medications is considered. Anticoagulation and antiplatelet therapy may need to be adjusted for some clinical conditions. Some types of infection, especially bacteremia, are associated with a higher incidence of stroke due to increased endothelial activation and platelet aggregation (Basra et al., 2009). Therefore, increased antiplatelet therapy may be warranted during systemic bacterial infections.

The major hemodynamic effects of a continuous-flow LVAD are increases in diastolic pressure and flow (Myers et al., 2009). Because these devices pump continuously throughout the entire cardiac cycle, aortic flow is also present during diastole when normal pulsatile flow is absent. The pulse pressure is influenced by left ventricular contractility, intravascular volume, pre-load and after-load.
pressure, and by pump speed. Owing to the reduced pulse pressure during continuous-flow LVAD support, it is often difficult to palpate a pulse and measure blood pressure accurately by the usual auscultatory or automated methods. After the arterial catheter is removed, the arterial blood pressure is most reliably assessed using Doppler and a sphygmomanometer. Arterial blood pressure might be controlled with vasoactive and inotropic medications and intravascular fluid volume management. The pump speed should not be adjusted to achieve a desired arterial blood pressure. The goal is to maintain the mean arterial blood pressure in the range of 70 to 80 mm Hg. It should not exceed 90 mm Hg. Unlike a pulsatile LVAD, the amount of cardiac output support by a continuous-flow pump is affected by the after-load, or systemic vascular resistance. Maintaining the mean arterial pressure in the desired range will optimize cardiac support. Hypertension is controlled to avoid decreased LVAD support and cardiac output as well as to avoid cerebrovascular events. Immobilizing the percutaneous lead to prevent exit site trauma reduces infection risk. Care of the percutaneous lead and exit site must be a priority for successful outpatient care (Slaughter et al. 2010). Multidisciplinary teams are required that allow close collaboration between cardiologists, medical specialists, and cardiac surgeons. The HF specialist must participate in managing these teams. The HF specialist should be familiar with the need to evaluate right ventricular function and associated tricuspid regurgitation prior to placement of an LVAD. Compared with successful cardiac transplantation, exercise capacity is lower following chronic outpatient mechanical support and the patient’s daily concerns are typically greater (e.g., battery exchange or recharging, driveline maintenance). A key point in postoperative device management is paying attention that continuous-flow LVADs do not contain valves. If the pump stops, there may be back flow, which can have severe consequences (similar to aortic insufficiency), so we must avoid power interruption or inadvertent power lead disconnection that would lead to loss of support. Pump speed optimization and device monitoring present unique challenges compared with pulsatile devices, because continuous-flow pumps can generate large negative pressures at the pump inlet, which may result in septal shift or ventricular collapse. It is also important to avoid setting the pump speed too high, which can result in ventricular collapse or inlet obstruction and initiate arrhythmias (ACCF/AHA/ACP/HFSA/ISHLT 2010 Clinical Competence Statement on Management of Patients With Advanced Heart Failure and Cardiac Transplant). The system-provided parameters of speed, power, pulsatility index, and estimated flow in conjunction with echocardiography serve as the primary indicators of proper device function. The patient’s clinical status should always be assessed when device function is evaluated. Successful long-term LVAD support depends on comprehensive care from a multidisciplinary team, including the patient and his or her family member(s)/caregiver(s). Training on proper self-care and system operation, with an emphasis on meticulous care of the percutaneous lead and exit site, should begin preoperatively. Training continues throughout hospitalization. Eventually, the patient’s demonstration of understanding and competency may be a requirement for discharge.

11. References


European Society of Cardiology; Heart Failure Association of the ESC (HFA); European Society of Intensive Care Medicine (ESICM), Dickstein K, Cohen-Solal A, Filippatos G et al. (2008). ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in
collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur J Heart Fail. 2008;10(10):933-89.


The assist devices will continue adding a large number of years of life to humans globally and empower the medical society to optimize heart failure therapy. While expensive and cumbersome task, the foundation provided in this book reflects a contemporary product of original research from a multitude of different experts in the field. We hope this cumulative international effort provides the necessary tools for both the novice as well as the active practitioner aiming to change the outcome of these complex patients.

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