Chapter 2

Heart Transplant: Current Indications and Patient Selection

Ulises López-Cardoza, Carles Díez-López and José González-Costello

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.75507

Abstract

Heart transplant remains the gold standard treatment for end-stage heart failure, in spite of the recent advances in pharmacological treatment and device therapy. As expected, since the first heart transplant was performed 50 years ago, outcomes in heart transplant have continued to improve over the last decades focusing on perioperative management, the availability of newer and better mechanical circulatory support before and after heart transplant and immunosuppressive drug development. Nonetheless, in the last years we have witnessed a significant drop in the heart donor's pool as the greatest limiting factor, coupled with a rising number of advanced heart failure patients. Moreover, the difficulty in handling these patients, with multiple and more complex comorbidities, is continuously increasing. More importantly and despite these difficulties, conditional half-life in transplanted patients has nowadays reached 12 years of life expectancy. Thus, besides trying to increase donor numbers, candidate selection emerges as one of the most challenging issues for heart transplant programs. In this chapter we review the latest knowledge on indications for heart transplant, as well as the available screening and optimization tools in candidate selection in order to continue improving outcomes.

Keywords: heart transplant, indications, advanced heart failure, ventricular assist device

1. Introduction

Heart transplant (HTx) is indicated in patients with stage D heart failure (HF) who remain with severely disabling symptoms in spite of optimal medical and device treatment, and where other surgical options have been excluded [1]. In patients with progressive HF, treatment

optimization by selection and up-titration of appropriate drugs (e.g., beta-blockers and inhibitors of the renin-angiotensin-aldosterone axis), device implantation (resynchronization therapy, implanted cardioverter defibrillator), and surgical intervention if appropriate (e.g., valve replacement in case of valve disease) becomes mandatory. Only in cases where conventional HF treatment is not well tolerated and/or the patient presents an unfavorable course we will raise the option of HTx. At this point, it is useful to recognize the clinical and hemodynamic parameters that identify patients in an advanced-HF (AHF) situation (**Table 1**), which represents 5% of the total number of patients in HF [2]. In the case of patients in cardiogenic shock (CS), the priority is to get the patient out of the shock situation and correct multi-organ failure, for which we will usually need inotropic and vasoactive treatment, intra-aortic balloon counterpulsation and, in some cases, ventricular mechanical assistance devices (VAD). Once the patient is stable, we will have to attempt to wean the VAD, if we consider that myocardial recovery is an option, or HTx otherwise.

The long waiting times and the increasing number of unstable patients have favored the development of mechanical circulatory support (MCS) therapies as bridge to transplant (BTT) and bridge to candidacy or decision (BTC/BTD). This was initially achieved by the use of short-term ventricular assist devices (STVADs), but in the last decades long-term ventricular assist

1. Severe symptoms of heart failure with dyspnea and/or fatigue at rest or on minimal exertion (NYHA functional class III or IV)
2. Episodes of fluid retention (pulmonary and/or systemic congestion, peripheral edema) and/or of reduced cardiac output at rest (peripheral hypoperfusion)
3. Objective evidence of severe cardiac dysfunction, shown by at least 1 of the following
a. Low left ventricular ejection fraction (<30%)
b. Pseudonormal or restrictive mitral inflow pattern on Doppler echocardiography
c. High left ventricular filling pressures (mean PCWP >16 mmHg, and/or mean RAP >12 mmHg by pulmonary artery catheterization)
d. High natriuretic peptide levels, in the absence of non-cardiac causes
4. Severe impairment of functional capacity shown by 1 of the following:
a. Inability to exercise
b. 6-minute walk test ≤300 m or less in females and/or patients aged ≥75 years
c. Peak oxygen consumption <12 to 14 mL/kg/min
5. History of ≥1 heart failure hospitalization in the past 6 months
6. Presence of all the previous features despite "attempts to optimize" therapy including diuretics, renin-angiotensin-aldosterone system inhibitors, and beta-blockers, unless these are poorly tolerated or contraindicated, and cardiac resynchronization when indicated
NYHA: New York Heart Association; PCWP: pulmonary capillary wedge pressure; RAP: right atrial pressure.

Table 1. Definition of advanced heart failure according to ESC (Adapted from Metra et al. [2]).

devices (LTVADs) have been developed and allow for longer periods of support. Because recovery of the ventricular dysfunction is possible, especially in some settings such as myocarditis or acute coronary syndrome, the bridge to recovery (BTR) strategy is another option. Finally, the development of more reliable LTVADs has created the possibility of destination therapy (DT) in patients who are not candidates for HTx because of significant comorbidities. In this chapter we will focus our attention in the use of LTVADs as a bridge to transplant.

When evaluating a patient for HTx, we must assess the following aspects:

1. What is the expected mortality of the HF patient with the maximal surgical and medical treatment options?
2. What is the risk of performing a HTx? Which are the potential complications derived from the medical and immunosuppressive treatment after the intervention?
3. Who is the appropriate candidate? When should we put the patient on the waiting list for HTx?
4. How can we optimize our patient before HTx in order to improve post-operative outcomes?

2. Assessing prognosis of the patient with HF

In spite of the recent treatment advances, HF mortality is expected to be around 10% per year in large randomized studies [3], with a median survival of approximately 2 years in unselected cohorts [4]. Because mortality during the first year post-HTx ranges between 12 and 20% and the median of survival of the heart transplant is 12 years [5], it is important to carry out an adequate prognostic stratification in order to select those patients who will obtain the maximum benefit from HTx. Along these lines, we will review the most important clinical features and risk factors that should direct clinicians to undergo an early and comprehensive evaluation, and confirm if the patient is an appropriate candidate for the available advanced therapies, before a more severe deterioration is present and treatment options become compromised.

2.1. Clinical parameters

Multiple clinical parameters are associated with higher mortality in HF patients. During the last years, there has been a considerable effort by clinicians to define the common characteristics of AHF, and these can be seen in **Table 1**. For instance, progressive treatment intolerance, persistent clinical signs of HF, echocardiographic and hemodynamic signs of low output, multiorgan involvement and repeated hospitalizations, severely compromise patients' prognosis [6].

2.2. Etiology of heart failure

Ischemic cardiomyopathy has traditionally been associated with higher mortality, especially when severe left ventricular dysfunction and three-vessel or main stem left coronary artery

disease unsuitable for revascularization is present [7]. Congenital heart diseases are also associated with greater mortality because of the higher degree of pulmonary arterial hypertension and possible previous cardiac surgeries [5]. Therefore, we recommend referring these patients to specific transplant centers with congenital heart disease expertise.

Cardiomyopathies are disorders in which the heart muscle is structurally and functionally abnormal in the absence of other causes such as coronary artery disease, arterial hypertension, valvular heart disease, congenital heart disease or any other condition that may cause abnormal loading conditions. In idiopathic dilated cardiomyopathies, the presence of a higher degree of fibrosis demonstrated by delayed gadolinium enhancement in cardiac magnetic resonance (MRI) is associated with worse prognosis and sudden death [8]. T1 and T2 mapping are MRI-based techniques that are able to measure the extracellular volume in the heart, which have also been shown to correlate with prognosis in patients with HF and cardiomyopathies [9].

Moreover, a non-negligible number of patients are affected by familial dilated cardiomyopathy (DCM), which can sometimes be easily identified with a simple family pedigree [10]. On this subject, with the advent of next generation sequencing gene techniques, we are now able to identify multiple mutations associated with DCM in more than 50 genes [11]. The most frequent ones are titin (TTN), lamin (LMNA) and desmin (DES). Pathogenic mutations in LMNA [12] and DES [13] as well as filamin C (FLNC) [14] genes are specifically related with frequent arrhythmias and subsequent worse prognosis. Therefore, genetic testing should also be taken into account when stratifying patients, especially because they usually affect young individuals, with less evident HF symptoms in spite of the severe myocardial disease.

The indication for HTx in patients with hypertrophic cardiomyopathy (HCM) is unusual and should be reserved for patients with persistent marked symptoms, after all therapeutic possibilities have been applied, including septal reduction techniques. It is more frequent to perform HTx in patients with HCM with progressive severe left ventricular dysfunction and/or a restrictive pattern.

Arrhythmogenic cardiomyopathy is produced by the alteration of cardiac desmosomes, which predisposes to an abnormal response to mechanical stress. Genetically, it is transmitted predominantly in an autosomal dominant manner with a variable clinical expression and an incomplete penetrance that is dependent of age. It is a frequent cause of sudden death and ventricular arrhythmias, especially in young adults and athletes, because it is linked to severe ventricular arrhythmias, especially when it affects the left ventricle. Furthermore, in spite of the use of implantable cardiac defibrillators (ICD), severe cardiac events including sudden cardiac death and mortality might appear over time, because of progressive biventricular dysfunction and untreatable arrhythmias. Hence, HTx should always be taken into account during follow-up [13, 14].

Restrictive cardiomyopathy (RCM) is the least common and it comprises a group of diseases of the myocardium, characterized by a rigid myocardium that produces diastolic dysfunction that leads to a restrictive physiology, with a normal or reduced systolic and diastolic ventricular volumes and non-thickened or minimally thickened ventricular walls. The majority of the restrictive cardiomyopathies can be secondary to a toxic process (e.g., radiotherapy,

hypereosinophilic syndrome, use of anthracyclines), infiltrative disease (e.g., amyloidosis or sarcoidosis), and storage cardiomyopathy (Anderson-Fabry disease, Danon disease, hemochromatosis) with amyloidosis being the most common etiology. Nonetheless, genetic restrictive cardiomyopathy is also a diagnostic possibility that should be taken into account, especially when family involvement is present. In this regard, DES mutations are characterized by severe diastolic dysfunction and atrio-ventricular block, with progressive systolic dysfunction and early-onset end-stage HF, and frequent neuromuscular disease.

In regards to amyloidosis, it is important to distinguish between the different types of amyloid deposit because of the different prognosis and treatment strategies. In immunoglobulin light chain amyloidosis (AL or primary amyloidosis) the evolution of HF is very fast, and although HTx is feasible, significant involvement of other organs should be ruled out. Nonetheless, HTx outcomes are significantly worse, even with bone marrow transplant, and survival rates reach 82% and 65% at 1 and 5 years, respectively [15, 16]. In cases of hereditary transthyretin amyloidosis, HF does not progress as rapidly as in light chain amyloidosis, and it is recommended to perform HTx followed by liver transplant at a second time point to prevent further myocardial compromise, although the advent of new drugs to treat transthyretin amyloid and the different mutations involved may change this strategy. In any case, it is also essential to exclude severe amyloid involvement of other organs [17].

Among the different types of cardiomyopathies, serious multi-organ involvement, particularly neuromuscular involvement that could compromise the respiratory capacity should always be ruled out. Thus, the decision to go to HTx must be taken after a comprehensive multidisciplinary evaluation that should involve at least, a HF specialist, a pneumologist and a neurologist.

2.3. Functional capacity

Clinical assessment of functional capacity is a subjective measure of the patient's ability to perform daily activities that can easily be obtained, and correlates with the severity of the disease. It is measured by the New York Heart Association (NYHA) scale, which stratifies four groups (functional class) from less to more limitations in physical activity. Candidates for HTx are most of the time in functional class IV despite optimal medical treatment (stage D of the American Heart Association classification), although they can alternate with some periods of partial recovery to functional class III.

In spite of its usefulness, this scale is a subjective measure that an change depending on the patient and physician's interpretation, and should be complemented by the use of more objective tests. The cardiopulmonary exercise test (CPET) measures peak oxygen uptake (VO2), which is the most accurate measure of exercise capacity and cardiopulmonary performance [18]. According to the latest guidelines, a peak VO2 ≤ 14 mL/kg/min or peak VO2 ≤ 12 mL/kg/min in the presence of β-blockers at maximal exertion should be used to include patients in HTx list, although this should not be the unique parameter. In cases of a sub-maximal cardiopulmonary exercise test, defined as the ratio of carbon dioxide output/oxygen uptake (also called respiratory exchange ratio [RER]) < 1, the use of ventilation to carbon dioxide slope (VE/VCO2) > 35 is also useful because of its prognostic value [19].

Also, the 6-minute walking test (6'WT) measures the distance that the patient is able to walk in 6 minutes and is useful when a cardiopulmonary test is not available. A walking distance of less than 300 m is associated with an annual mortality above 50% [20], and is one of the criteria of AHF.

2.4. Risk scores

Currently, there are several risk scores available that might help in patient stratification, and give support in decision making. In ambulatory patients, there are two risk scores that complement the prognostic information obtained from CPET:

1. The Seattle Heart Failure Model (SHFM) has 21 variables; it is derived from a study of 1125 patients with NYHA class IIIB or IV, during the Prospective Randomized Amlodipine Survival Evaluation (PRAISE) [21]. It was used in the REMATCH trial cohort for predicting 1-year mortality in the medical and LTVAD groups with good accuracy [22]. The model was also prospectively validated in five additional cohorts consisting of 9942 HF patients and 17,307 person-years of follow-up [23]. When an estimated 1-year survival of less than 80% is obtained, patients should be considered for HTx [19].
2. The Heart Failure Survival Score (HFSS) is calculated with the following variables: VO2 max, ejection fraction of the left ventricle, sodium, mean arterial pressure, ischemic etiology, resting heart rate, QRS > 120 ms. Patients in the medium and high risk category should be considered for advanced-HF therapies such as HTx listing or VAD implantation [24].

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) is a database created in 2006, with information of more than 15,000 patients who received an MCS [25]. The INTERMACS classification was created from this registry and helps to stratify patients in an AHF situation, see **Table 2**. In this regard, patients in a higher INTERMACS profile (1 or 2) seem to have worse post-HTx outcomes than those in better pre-operative condition (INTERMACS 3-4) [26].

2.5. Hemodynamic parameters

Pulmonary hypertension (PHT) is defined by a mean pulmonary arterial pressure greater than 25 mmHg, and usually develops in response to a passive backward transmission of elevated filling pressures from the left ventricle. Nonetheless, irreversible PHT might eventually develop in response to chronic elevated pressures that cause vascular remodeling, and is closely related to primary graft failure (PGF) due to right ventricular failure (RVF), which carries an elevated mortality after HTx [28]. Therefore right heart catheterization is recommended before HTx and should be done periodically, every 3–6 months [19], especially if reversible PHT has been previously confirmed.

The main direct (measured directly during procedure) and indirect (calculated from direct parameters) parameters evaluated during right heart catheterization are:

- Direct parameters: 1-right atrial pressure, 2-sistolic pulmonary arterial pressure (SPAP), 3-mean pulmonary arterial pressure (MPAP), 4-pulmonary capillary wedge pressure (PCWP), and 4-cardiac output (CO).
- Indirect parameters: 1-transpulmonary gradient (TPG): Defined as the difference between mean pulmonary arterial pressure and capillary wedge pressure (TPG = MPAP-PCWP), 2-pulmonary vascular resistance (PVR) defined as TPG/CO is usually expressed in Wood units, 3-cardiac index expressed as the result of CO/body surface area.

Reversible PHT is defined as a drop in SPAP < 50 mmHg, TPG < 12 mmHg and PVR < 3 Woods units after optimization of cardiac index and loading conditions (indicated mainly by central venous pressure, systemic vascular resistance and systemic arterial pressure) by the use of intravenous diuretics, inotropes and vasodilators, if necessary. A combination of inotropes with direct vasodilators (e.g., dobutamine and nitroprusside) and selective vasodilators (e.g., sildenafil, nitric oxide) is also commonly used. It is important to mention that if after the pulmonary vasodilation test the PVR drops <3 UW but the systolic blood pressure falls to less than 85 mmHg, there is still a high risk of PGF after HTx [29, 30].

In any case, but especially when irreversible or fixed PHT is present, it is important to rule out concomitant pulmonary disease, obstructive sleep apnea syndrome or chronic pulmonary

INTERMACS level	Description	1 year survival with LTVAD
1. Cardiogenic Shock ("crash and burn")	Hemodynamic instability with increasing inotropic and vasopressor support, and critical hypoperfusion of target organs.	52.6 ± 5.6%
2. Progressive decline despite inotropic support ("sliding fast" on inotropes)	Dependent on inotropic support but continues with signs of clinical deterioration (worsening renal failure, nutritional depletion, and inability to restore volume balance).	63.1 ± 3.1%
3. Stable but inotrope-dependent ("dependent stability")	Stable with low/intermediate doses of inotropes, but necessary due to arterial hypotension, progressive renal failure, worsening symptoms	78.4 ± 2.5%
4. Resting symptoms on oral therapy ("frequent flyer")	Patient at home on oral therapy but with high doses of diuretics and frequent symptoms of congestion at rest or with regular activity	78.7 ± 3%
5. Exertion intolerant ("housebound")	Comfortable at rest but unable to engage in any activity	93 ± 3.9%
6. Exertion limited ("walking wounded")	Comfortable at rest and without symptoms during daily living activities, but who becomes symptomatic with any meaningful physical exertion	
7. Advanced NYHA class III ("placeholder")	Patient in NYHA class III with no recent episode of acute decompensation	

NYHA: New York Heart Association.

Table 2. INTERMACS patient profile (Source Ponikowsky et al. [27]).

thromboembolism. If there is no responsible pulmonary disease, there are several studies that have shown that the chronic use of bosentan or sildenafil might reduce PHT and acheive reversibility of PHT after 3–4 months of this therapy [31]. If despite an appropriate vasodilator treatment there is no reversibility of the PHT, LTVAD therapy should be considered, together with selective vasodilator treatment (usually sildenafil) [32].

3. Ventricular assist devices as bridge to transplant

MCS has largely evolved over the last years and nowadays it constitutes a real option for patients in AHF situation, especially in those who are in INTERMACS 1 to 4 profiles. As a matter of fact, in 2000, the International Society of Heart and Lung Transplantation (ISHLT) reported that 19.1% of HTxs were mechanically supported, and by the year 2012 this number had increased to 41% [33]. Lately, the clinical outcomes of a Spanish registry of 291 patients supported by STVAD as a BTT strategy have been published, showing an overall survival rate from listing to hospital discharge of 61%, and 1-year survival after listing of 58% [34]. Although there was a significant mortality rate, it is important to mention that the majority of patients were in an emergency situation (INTERMACS 1-2) and were supported by a very heterogeneous group of STVADs. Accordingly, it seems reasonable to use LTVADs as a BTT strategy at an early stage of the disease (INTERMACS 3-4) to improve HTx outcomes.

Irrespective of the design, LTVAD unloads the heart by pumping blood from the left ventricle to the aorta. Technology of LTVADs has been continuously evolving since the creation of the first generation devices, which had a diaphragm and unidirectional valves to replicate the pulsatile cardiac cycle. The HeartMate XVE was approved by the FDA; first as BTT in 1998 and in 2002 as a DT, after the publication of the REMATCH trial. Later advances in technology have been directed to minimize the size of the pump and to increase its durability. Nowadays, continuous flow LTVADs have substituted pulsatile devices; these utilize a permanent magnetic field designed to rapidly spin a single impeller supported by mechanical, hydrodynamic or magnetic bearings. In second-generation continuous flow LTVAD the impeller outflow is directed parallel to the axis of rotation (e.g., Heartmate II, Thoratec and Incor, Berlin Heart) while in the third generation devices the impeller outflow is directed perpendicular to the axis of rotation (e.g., HVAD, Medtronic and HeartMate 3, Abbot). Third generation pumps have lower risk of suction events, more pulsatile waveform, and more precise flow estimation than second-generation pumps, but pump flow has a higher dependency on loading conditions [35].

The best candidates for a BTT strategy are patients in INTERMACS 3-4 profile; especially if a long waiting time for HTx is expected, as it avoids further deterioration, allows clinical optimization, and provides a better quality of life. In this regard, some factors that may increase the difficulty in finding a appropriate donor should be taken into consideration, as for example previous allosensitization or large body size.

BTC LTVAD strategy is the preferred option for those patients with relative contraindications to HTx that could be potentially reversible with hemodynamic support. For instance, most patients with initially irreversible PHT reach reversibility or even normal pulmonary

pressure after some months with LTVAD [24]. In a similar fashion, renal dysfunction due to cardiorenal syndrome can improve enough to consider HTx. In this group, we can also include patients with recently diagnosed cancer or obesity (BMI > 35 kg/m^2), in which the implantation of a LTVAD could give them time to re-evaluate candidacy.

Regarding LTVAD as DT, one of the limitations of this strategy is the increase in adverse events associated with long-term use of LTVAD. The ROADMAP study took a sample of 200 patients in INTERMACS 4–7 and divided them into two groups: optimal medical management (OMM) or OMM plus LTVAD. The final result showed an improvement in functional capacity in the second group but with a significant increase in adverse events, especially hemorrhagic complications [36]. Although current indications for DT consider a more advanced profile of patients (criteria derived from the REMATCH and HeartMate II DT trials [37]), the results of the ROADMAP study give us and idea of the advantages and disadvantages of the use of LTVAD as DT, further supporting the fact that HTx remains the ideal therapy in this population.

Regardless of the selected strategy, the most important fact is to ensure a correct selection of candidates for LTVAD implantation. One of the tools used to predict outcomes of these patients using mechanical support is the HeartMate II Risk Score, which is derived from an analysis of the HeartMate II registry. Briefly, it is based on five variables (age, serum albumin, creatinine, INR, and center volume of LVAD) used to create an equation that predicts mortality at 90 days [38]. Moreover, because LTVADs only support the left ventricle, one of the critical points to take into consideration is the potential right ventricular failure (RVF) after MCS is initiated. Nowadays, there are no comprehensively evaluated tools to predict RVF, but some hemodynamic and echocardiographic parameters might be useful. Concerning hemodynamic evaluation, a right ventricular stroke work index less than 250 mmHg·mLm^2 [39], right atrial pressure > 15 mmHg and central venous pressure/PCWP >0.63 are considered important risk factors of RVF [40]. Echocardiographic parameters include tricuspid annular motion (TAPSE) < 7.5 mm [41], right ventricular to left ventricular end diastolic diameter ratio > 0.72 [42], severe tricuspid regurgitation, right ventricular short/long axis ratio > 0.6 [43] and right ventricular free wall strain [44]. A biventricular approach using continuous blood flow pumps has recently been reported with limited success considering the significant number of adverse events during follow-up [45].

Finally, it is very important to ensure optimal patient's self-care training by specialized nurses, and appropriate follow-up is indispensable for the success of a LTVAD program. Daily care of the device, especially considering the correct management of the driveline wound is of paramount importance to avoid infection. Moreover, the correct management of concomitant cardiovascular risk factors such as hypertension or diabetes, and other comorbidities is also a relevant issue in these patients that should be pursued.

4. Inclusion in heart transplant waiting list

The decision of including a patient in the HTx waiting list is not easy and should be taken together by a medical and surgical team, in a case-by-case comprehensive evaluation. Only

stage D HF patients without any other treatment option should be evaluated for HTx, because of the shortage of organs, the intrinsic risk of surgery, and the risk of rejection and complications due to immunosuppressant therapy. **Table 3** shows the indications for HTx.

Therefore, it is important to undergo an exhaustive study of the patient before listing for HTx, in order to exclude any significant risk factor that might compromise outcomes after HTx. Last but not least, the patient must be motivated, well informed and in an optimal psychological state to follow the intensive pharmacologic treatment that follows the HTx. **Table 4** shows recommended studies that should be done when evaluating candidacy for HTx.

To conclude, patients with LTVAD as BTC can be included in the waiting list once reversible PHT is confirmed by a right heart catheterization, and/or there is significant improvement in renal function (glomerular filtration rate [GFR] > 30 cc/min/1.73 m^2, especially if there is no evidence of intrinsic renal damage: absence of significant proteinuria without significant abnormalities in renal ultrasonography), and other parameters. In patients with concomitant treated malignant neoplasm, a thoughtful evaluation tackling life expectancy and relapse possibilities, together with an oncologist's evaluation should be performed before listing for HTx.

Absolute Indications
1. Hemodynamic compromise due to HF
· Refractory cardiogenic shock
· Documented dependence on IV inotropic support to maintain adequate organ perfusion
2. Peak VO2 less than 14 mL per kg per minute with achievement of anaerobic metabolism or less than 12 mL per kg per minute with the use of β-blockers
3. Severe symptoms of ischemia that consistently limit routine activity and are not amenable to coronary artery bypass surgery or percutaneous coronary intervention
4. Recurrent symptomatic ventricular arrhythmias refractory to all therapeutic modalities
Relative Indications
1. In the presence of sub-maximal cardiopulmonary exercise test (RER<1.05), ventilation equivalent of carbon dioxide (VE/VCO2) slope > 35
2. Use of prognostic scores in conjunction with cardiopulmonary exercise stress test. A 1-year estimated survival calculated by the SHFM less than 80% and a HFSS in high/medium risk range
3. Recurrent unstable ischemia not amenable to other intervention
4. Recurrent instability of fluid balance/renal function not due to patient noncompliance with medical regimen
Insufficient indications
1. Low left ventricular ejection fraction
2. History of NYHA functional class III or IV symptoms of HF
3. Peak VO2 greater than 15 mL per kg per minute (and greater than 55% predicted) without other indications
V02: Oxygen consumption; SHFM: Seattle Heart Failure Model; HFFS: Heart Failure Survival Score; NYHA: New York Heart Association.

Table 3. Heart transplant indications (Source Kirklin JK et al. and Hunt S et al. [46, 19]).

- Clinical history and complete physical examination
- Size/weight/body mass index
- Blood Typing and Immune suitability study

· ABO blood group

· HLA typing

· Panel-reactive antibody (PRA)

· Flow cytometry (Luminex)

- Assessment of severity of cardiac insufficiency
- Multiple organ function evaluation

· General analysis with glycemia, lipid profile, renal function, hepatic profile, coagulation, thyroid hormones, natriuretic peptides

· First-hour urinalysis with proteinuria

· Chest x-ray

· Functional respiratory tests with arterial gases

· Abdominal ultrasound or thoraco-abdominal CT scan

· Doppler echo of supra-aortic trunks (if more than 50 years, diabetic, ischemic cardiomyopathy or clinical suspicion)

· Lower extremity ankle/arm or Doppler echo index (if more than 50 years, diabetic, ischemic cardiomyopathy or clinical suspicion)

· Electroencephalogram

· Bone densitometry (if more than 50 years, woman or clinical suspicion)

- Infectious assessment

· Hepatitis B virus: surface antigen, antibody of surface, anti-core

· Antibody hepatitis C virus

· Antibody hepatitis A virus

· Human immunodeficiency virus

· VDRL (venereal disease research laboratory)

· Herpes Simplex antibody

· Cytomegalovirus antibody

· Toxoplasma antibody

· Epstein–Barr antibody

· Varicella antibody

· Tuberculin or quantiferon test

- Vaccination

· Influenza (annual)

· Hepatitis B and A if it has not been done

· Pneumococcal vaccine (every 5 years)

- Study of hidden malignant neoplasm

· Fecal occult blood test × 3

· Colonoscopy (if >50 years old)

· Mammography (if indicated or > 40 years)

· Gynecological examination and vaginal cytology (if >18 years old and sexually active)

· Specific prostate antigen and rectal examination (men >50 years old)

- Other evaluations

· Social worker

· Psychiatry

· Psychosocial and economic assessment

HLA: human leucocyte antigen and CT: computerized tomography.

Table 4. Recommended studies in the evaluation of candidates for HTx. Adapted from Mehra et al. [29].

4.1. Immune suitability evaluation

Screening for humoral rejection is done through the panel-reactive antibody (PRA) test, which determines the presence of circulating anti-HLA antibodies. With this cytotoxic test, it is possible to estimate the sensitization of the recipient by the percentage of the serum reactivity that activates complement against a panel of the most common HLAs in the recipient's country. A PRA > 10% is considered positive and is a relative contraindication for HTx. In these cases, it is recommended to perform a prospective cross-match between the lymphocytes of the donor and recipient's serum before HTx. Currently, it is also possible to identify

and quantify the amount of antibodies against surface HLA antigens using a flow cytometry immunofluorescence technique. This method (Luminex) is much more sensitive than the PRA and allows a better assessment of the risk of positive cross-reactivity at the time of HTx and eventual humoral rejection.

Patients can be sensitized after pregnancies, blood transfusions, after previous transplantation or after the implant of a ventricular assist device, although sometimes there is no obvious sensitizer event, and it is thought to be due to cross-reactivity between bacterial or viral epitopes and HLAs. In case that the recipient has a ventricular assist device, it is recommended to repeat the PRA and flow cytometry every 2–3 months. If blood transfusions are required, the PRA and flow cytometry should be repeated 2 weeks after the transfusion and each month during 6 months [29].

The presence of anti-HLA antibodies with high levels of median fluorescent intensity or MFI (units used to quantify antibodies), usually over 3000–5000, depending on the immunology laboratory, is considered potentially cytotoxic. By this technique it is also possible to obtain a calculated PRA (cPRA), which gives the percentage of unacceptable HLAs in the donor population. For example, if the cPRA is 80%, it means that only 20% of all possible donors in this specific population will be compatible with the receptor. Although the cPRA cut-points are not clearly established, some authors consider an absolute contraindication if cPRA is above 50–70%, and thus recommend a desensitization therapy before HTx [47]. In these cases it is also necessary to perform a virtual cross-match at the time of HTx, consisting of the evaluation of anti-HLA receptor antibodies titters relative to the donor HLA. If the virtual cross-match is positive, the risk of hyperacute rejection is very high and the donor organ must not be accepted.

5. Infectious evaluation and vaccination

A complete serologic status of the potential recipient should always be obtained before HTx, especially considering previous exposure to cytomegalovirus and Mycobacterium tuberculosis, as it is crucial when defining infectious prophylaxis after HTx.

The human immunodeficiency virus infection with undetectable viral load is not a contraindication to HTx at present, although each case must be assessed individually and retroviral treatment should be adapted to avoid interference with calcineurin inhibitors [48].

Patients with chronic hepatitis B infection (defined by the presence of hepatitis B surface antigen) have equal survival rates compared to the rest of the cohort, unless there is significant liver disease. In this setting, liver cirrhosis should be ruled out with biopsy if necessary, and antivirals should be given in order to lower viral load, since there is a risk of reactivation of the disease with immunosuppression after HTx. Similarly, when hepatitis C virus serology is positive, the quantitative viral load and degree of liver disease must be determined. If circulating HCV is detected, the disease is active and antiviral treatment must be prescribed to eliminate the virus. An altered hepatic function, which is not justified by HF, or a liver biopsy with evidence of cirrhosis, should be considered an absolute contraindication [30].

Finally, vaccination against hepatitis A and B viruses is also recommended if not previously given, as well as vaccination against Pneumococcus (every 5 years), Influenza (annual) and *Haemophilus influenzae* before the HTx [29].

6. Risk factors and contraindications

Absolute contraindications for HTx are progressively diminishing because of the improved treatment strategies both for comorbidities and immunosuppressive therapies after HTx, so nowadays it is preferable to talk about risk factors that increase post-HTx morbidity and mortality than contraindications. According to the latest recommendations from the ISHLT [19] the most important HTx risk factors are classified in **Table 5**. Nonetheless, it is important to especially consider the following:

- Patients with age > 70 years could be considered for HTx based on individual evaluation. It is important to take into consideration that this population has lower rates of rejection but higher mortality than younger patients.
- Patients with a body mass index (BMI) > 35 kg/m^2 should wait until they achieve a BMI ≤ 35 kg/m^2 to be included in the waiting list, because patients with BMI > 35 kg/m^2 have more difficulty in finding an adequate donor. Besides, there is some evidence that this group of patients have an increase in post-operative morbidity and mortality.
- Poorly controlled diabetes (glycosylated hemoglobin [HbA1c] >7.5% or 58 mmol/mol) with end-organ damage (other than non-proliferative retinopathy) is a relative contraindication for HTx.
- Presence of irreversible renal dysfunction with GFR <30 cc/min/1.73 m^2 should be considered a relative contraindication for HTx alone, although the combination of heart and kidney transplant could be considered.
- Clinically severe symptomatic cerebrovascular disease could be considered a contraindication for HTx based on the existence of a study that shows how these patients have an increased risk of stroke and functional decline as an independent variable after transplantation [49]. Peripheral vascular disease that limits rehabilitation without possibility of revascularization continues to be a contraindication.
- Frailty defined as a clinically identifiable disorder of amplified vulnerability of age-related decline in reserve and function across multiple physiologic systems brought on with minor stressors [50] should be assessed before HTx, the presence of three of five possible symptoms, including unintentional weight loss of 5 kg within the past year, muscle loss, fatigue, slow walking speed and low levels of physical activity define a fragile patient.
- Psychosocial evaluation previous to HTx is important in order to make sure that the patient is going to be able to accomplish an optimal care after transplantation. Absence of this condition is considered a relative contraindication.

Absolute contraindications

- Systemic disease with life expectancy <2 years:

· Active neoplasm (if preexisting, evaluation with an oncology specialist is necessary to stratify the risk of recurrence and establish a time to wait after remission)

· Systemic disease with multi-organ involvement (systemic lupus erythematosus, amyloidosis, sarcoidosis)

· Severe chronic obstructive pulmonary disease (FEV_1 < 1 L)

· Renal or hepatic severe dysfunction, if associated renal or liver transplant is not performed

- Irreversible pulmonary hypertension

· Pulmonary artery systolic pressure > 50 mmHg

· Transpulmonary gradient >12 mmHg

· Pulmonary vascular resistance >3 Wood units despite treatment

Relative contraindications

- Age > 70 years (carefully selected patients may be considered)
- Diabetes with end-organ damage (except non-proliferative retinopathy) or persistent poor glycemic control (HbA1c > 7.5%) despite treatment
- Active infection, except VAD infection. Patients with HIV, hepatitis, Chagas disease and tuberculosis can be considered with strict management
- Severe peripheral arterial or cerebrovascular disease not suitable for treatment
- Other serious comorbidities with poor prognosis, such as neuromuscular diseases
- Obesity: BMI > 35 kg/m^2
- Cachexia: BMI < 18 kg/m^2
- Frailty: when three of five possible symptoms (including unintentional weight loss of >5 kg within the past year, muscle loss, fatigue, slow walking speed, and low levels of physical activity) are present
- Current tobacco, alcohol or drug abuse
- Insufficient social support
- Elevated panel-reactive antibody test defined as >10%

FEV_1: forced expiratory volume in 1 s; VAD: ventricular assist device; HIV: human immunodeficiency virus; BMI: body mass index.

Table 5. Contraindications for heart transplant (Source Sanchez-Enrique et al. [51]).

7. Heart transplantation waiting list priority

Nearly 100,000 people worldwide have received a new heart since the first HTx 50 years ago, 8000 of them in Spain, which makes it a country with a remarkable experience [52]. Each year priority criteria on the waiting list are reviewed. The 2017 priority criteria in adult population in Spain are summarized in **Table 6**.

The objective of this model is to prioritize those patients in the most critical situation. The ASIS-TC study showed a median waiting time for patients in urgency Grade 0 of 7.6 days allowing HTx in nearly 80% of this population [34]. Other countries like the U.S have a more heterogeneous group of patients listed in emergency situation (Status 1A) (**Table 7**), which makes waiting times more prolonged, between 47 and 413 days, depending on the region

Urgency Grade 0: national (priority over the rest of grades**)**

- Patients with STVAD of complete support[a].
- Patients with extracorporeal membrane oxygenation (ECMO) or partial support STVAD for at least 48 hours if there is no evidence of multi-organ failure[b,c].
- Patients with dysfunctional LTVAD[d] secondary to mechanical dysfunction or thromboembolism.

Urgency Grade 1: regional (priority over elective patients in reference zone**)**

- Patients with a normally functioning external LTVAD[e].
- Patients with dysfunctional LTVAD secondary to driveline infection, gastrointestinal bleeding or right heart failure.

Elective

- Patients not included in Grade 0 or Grade 1 categories.

STVAD: short-term ventricular assist device; LTVAD: long-term ventricular assist device.[a]e.g., Levitronix Centrimag.
[b]e.g., Impella CP, Impella 5.0, Tandem Heart.
[c]Maximum time in urgency Grade 0 will be 7 days, once this time has passed the patient will be in Urgency Grade 1.
[d]e.g., BerlinHeart Excor, Hearmate II, Heartmate 3, Heartware HVAD.
[e]e.g., BerlinHeart Excor.

Table 6. Priority criteria for heart transplant donors in Spain (Adapted from barge et al. [53]).

[47]. This shows the importance of defining homogeneous criteria to define each stage of classification for HTx waiting list, especially in the setting of emergency. A new more precise classification for the U.S. is expected to be published in 2018.

Status code	Criteria
Status 1A	• ECMO • IABP • Inpatient TAH • Mechanical ventilation • Continuous infusion of a single high-dose intravenous inotrope or multiple intravenous inotropes, and with continuous hemodynamic monitoring of left ventricular filling pressures • LVAD, RVAD, or BiVAD for 30 days • Mechanical circulatory support with significant device-related complications (thromboembolism, device infection, mechanical failure, or life threatening ventricular arrhythmias)
Status 1B	• Uncomplicated LVAD, RVAD, BiVAD after 30 days have been used. • Outpatient TAH • Continuous infusion of intravenous inotropes
Status 2	• Candidates not meeting 1A or 1B criteria
Status 7	• Temporarily inactive, most often due to infection

BiVAD: biventricular assist device; ECMO: extracorporeal membrane oxygenation; IABP: intra-aortic balloon pump; LVAD: left ventricular assist device; RVAD: right ventricular assist device; TAH: total artificial heart.

Table 7. Status codes for heart transplantation in U.S. (Source Kittleson et al. [47]).

8. Conclusions

Cardiovascular diseases are the main cause of death around the world, and with the improvement in therapeutics leading to an increase of life expectancy it is probable that we will see increasing number of patients with HF. Also, prevalence of HF in the overall population ranges between 1 and 2% depending on the country. Therefore it is expected that the number of patients with AHF will continue rising after this review. Yet it is important keep in mind some concepts:

- Establishing HF etiology could play a key role in the management and prognosis of the patient and his family, especially if there is an identified genetic cardiomyopathy.
- NYHA scale is useful to determine functional capacity, however objective tests should be used in order to establish a more reliable prognosis in this population.
- Optimization of HF treatment with medication and devices according to the latest guidelines is mandatory before considering advanced therapies.
- LTVADs as BTT or BTC is an appropriate management strategy in selected cases, especially if they are in an INTERMACS 3 profile.
- HTx remains the optimal therapy for patients in stage D HF, however with the shortage of donors and the improvement in technology, LTVADs as DT might change the management strategy in developed countries.

Acknowledgements

We would like to thank Dr. Nicolás Manito and Dr. Josep Roca for their advice, tireless teaching and wisdom. Also Magda Nebot, Laia Rosenfeld and Carmen Mejuto for their invaluable daily work and support.

Conflict of interest

We declare no conflicts of interest in writing this chapter.

Appendices and nomenclature

HTx: heart transplant

HF: heart failure

http://dx.doi.org/10.5772/intechopen.75507

AHF: advanced heart failure

CS: cardiogenic shock

VAD: ventricular assist device

MCS: mechanical circulatory support

BTT: bridge to transplant

BTC: bridge to candidacy

BTD: bridge to decision

STVAD: short-term ventricular assist device

LTVAD: long-term ventricular assist device

BTR: bridge to recovery

DT: destination therapy

NYHA: New York heart association

PCWP: pulmonary capillary wedge pressure

RAP: right atrial pressure

DCM: dilated cardiomyopathy

HCM: hypertrophic cardiomyopathy

RCM: restrictive cardiomyopathy

CPET: cardiopulmonary exercise testing

VO2: oxygen uptake

VE/VC02: ventilation to carbon dioxide slope

RER: respiratory exchange ratio

6'WT: 6-minute walking test

SHFM: Seattle Heart Failure Model

HFSS: heart failure survival score

INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support

PHT: pulmonary hypertension

PGF: primary graft failure

RVF: right ventricular failure

SPAP: systolic pulmonary arterial pressure

MPAP: mean pulmonary arterial pressure

CO: cardiac output

TPG: transpulmonary gradient

PVR: pulmonary vascular resistance

ISHLT: International Society of Heart and Lung Transplantation

BMI: body mass index

HLA: human leucocyte antigen

PRA: panel-reactive antibody

BiVAD: biventricular assist device

ECMO: extracorporeal membrane oxygenation

IABP: intra-aortic balloon pump

LVAD: left ventricular assist device

RVAD: right ventricular assist device

TAH: total artificial heart

Author details

Ulises López-Cardoza, Carles Díez-López and José González-Costello*

*Address all correspondence to: jgonzalez@bellvitgehospital.cat

Advanced Heart Failure and Transplant Unit, Heart Disease Institute, Hospital Universitari de Bellvitge, IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain

References

[1] McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012 of the European society of cardiology. Developed in collaboration with the heart failure association (HFA) of the ESC. European Heart Journal. 2012;**14**:803-869. DOI: 10.1093/eurjhf/hfs105

[2] Metra M, Ponikowski P, Dickstein K, et al. Advanced chronic heart failure: A position statement from the study group on advanced heart failure of the heart failure Association of the European Society of cardiology. European Journal of Heart Failure. 2007;**9**:684-694. DOI: 10.1016/j.ejheart.2007.04.003

[3] Zannad F, McMurray JJ, Krum H, et al. Eplerenone in patiens with systolic heat failure and mild symtoms. The New England Journal of Medicine. 2011;**364**:11-21. DOI: 10.1056/NEJMoa1009492

[4] Jhund PS, Macintyre K, Simpson CR, et al. Long-term trends in first hospitalization for heart failure and subsequent survival between 1986 and 2003: A population study of 5.1 million people. Circulation. 2009;**119**:515-523. DOI: 10.1161/CIRCULATIONAHA.108.812172

[5] González-Vílchez F, Gómez-Bueno M, Almenar-Bonet L, et al. Registro español de trasplante Cardiaco. XXVIII Informe Oficial de la Sección de Insuficiencia Cardiaca de la Sociedad Española de Cardiología (1984-2016). Revista Española de Cardiología. 2017;**70**:1098-1109. DOI: 10.106/j.recesp.2017.07.032

[6] Setoguchi S, Stevenson LW, Schneewelss S. Repeated hospitalizations predict mortality in the community population with heart failure. American Heart Journal. 2007;**154**:260-266. DOI: 10.1016/j.ahj.2007.01.041

[7] Roig-Minguell E, Pérez-Villa F, Castel-Lavilla MA. Estudio y selección del receptor de trasplante cardiaco. In: Trasplante cardiaco. 1st ed. Pulpon LA, Crespo Leiro MG, editors. Buenos Aires: Editorial Médica Panamericana; 2009. 15-30 p

[8] Gulati A, Jabbour A, Ismali TF, et al. Association of fibrosis with mortality and sudden cardiac death in patients with nonischemic dilated cardiomyopathy. Journal of the American Medical Association. 2013;**309**:896-908. DOI: 10.1001/jama.2013.1363

[9] Radenkovic D, Weingärtner S, Ricketts L. T1 mapping in cardiac MRI. Heart Failure Reviews. 2017;**22**:415-430. DOI: 10.1007/s10741-017-9627-2

[10] Pinto YM et al. Proposal for a revised definition of dilated cardiomyopathy, hypokinetic non-dilated cardiomyopathy, and its implications for clinical practice: A position statement of the ESC working group on myocardial and pericardial diseases. European Heart Journal. 2016;**14-**37(23):1850-1858. DOI: 10.1093/eurheartj/ehv727. Epub 2016 Jan 19

[11] Hershberger RE, Morales A, Siegfried JD. Clinical and genetic issues in dilated cardiomyopathy: A review for genetics professionals. Genetics in Medicine. 2010;**12**:655-667. DOI: 10.1097/GIM.0b013e3181f2481f

[12] Captur G et al. Lamin and Heart. Heart. 2018;**104**(6):468-479. DOI: 10.1136/heartjnl-2017-312338

[13] Bermúdez-Jiménez FJ, et al. The novel desmin mutation p.Glu401Asp impairs filament formation, disrupts cell membrane integrity and causes severe arrhythmogenic left ventricular cardiomyopathy/dysplasia. Circulation. 2017;**137**(15):1595-1610. DOI: 10.1161/CIRCULATIONAHA.117.028719

[14] Ortiz-Genga MF et al. Truncating FLNC mutations are associated with high-risk dilated and arrhythmogenic cardiomyopathies. Journal of the American College of Cardiology. 2016;**68**(22):2440-2451. DOI: 10.1016/j.jacc.2016.09.927

[15] Roig E, Almenar L, González-Vílchez F, et al. Outcomes of heart transplantation for cardiac amyloidosis: Subanalysis of the spanish registry for heart transplantation. American Journal of Transplantation. 2009;**9**:1414-1419. DOI: 10.1111/j.1600-6143.2009.02643.x

[16] Arvidsson S, Pilebro B, Westermark P, et al. Amyloid cardiomyopathy in hereditary transthyretin V30M amyloidosis—Impact of sex and amyloid fibril composition. PLoS One. 2015;**10**:e0143456. DOI: 10.1371/journal.pone.0143456

[17] Lladó L, Fabregat J, Ramos E, Balletas C, Roca J, Casasnovas C. Sequential heart and liver transplantation for familial amyloid polyneuropathy. Medicina Clínica (Barcelona). 2014;**142**:211-214. DOI: 10.1016/j.medcli.2013.10.022

[18] Balady GJ, Morise AP. Mann DL, Exercise testing. In: Zipes DP, Libby P, Bonow RO, editors. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 10th ed. Philadelphia: Elsevier Saunders; 2015. p. 159

[19] Mehra MR, Canter CE, Hannan MM, et al. The 2016 International Society for Heart Lung Transplantation: A 10 year update. The Journal of Heart and Lung Transplantation. 2016;**35**:1-23. DOI: 10.1016/j.healun.2015.10.023

[20] Zugck C, Kruger C, Durr S, et al. Is the 6-minute walk test a reliable substitute for peak oxygen uptake in patients with dilated cardiomyopathy? European Heart Journal. 2000;**21**:540-549. DOI: 10.1053/euhj.1999.1861

[21] Pfeffer MA, Skali H. PRAISE (prospective randomized amlodipine survival evaluation) and criticism. JACC Heart Fail. 2013;**1**:315-317. DOI: 10.1016/j.jchf.2013.05.005

[22] Levy WC, Mozaffarian D, Linker DT, et al. Can the Seattle heart failure model be used to risk-stratify heart failure patients for potential left ventricular assist device therapy? Journal of Heart Lung Transplant. 2009;**28**:231-236. DOI: 10.1016/j.healun.2008.12.015

[23] Seattle Heart Failure Model. University of Washington [Internet]. 2107. Available from: https://depts.washington.edu/shfm/ [Accessed 2017-12-14]

[24] Mikus E, Stepanenko A, Krabatsch T, et al. Reversibility of fixed pulmonary hypertension in left ventricular assist device support recipients. European Journal of Cardio-Thoracic Surgery. 2011;**40**:971-977. DOI: 10-1016/j.ejcts.2011.01.019

[25] Kirklin JK, Naftel DC, Pagani FD, et al. Seventh INTERMACS annual report: 15000 patients and counting. The Journal of Heart and Lung Transplantation. 2015;**34**:1495-1504. DOI: 10.1016/j.healun.2015.10.003

[26] Fonarow GC, Adams KF, Abraham WT, et al. Risk stratification for in-hospital mortality in acutely decompensated heart failure: Classification and regression tree analysis. Journal of the American Medical Association. 2005;**293**:572-580. DOI: 10.1001/jama.293.5.572

[27] Ponikowski P, Voors AA, Anker SD, et al. 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. European Journal of Heart Failure. 2016;**18**. 2016:891-975. DOI: 0.1002/ejhf.592

[28] Rodríguez-Padial L, Escribano P, Lázaro M, et al. Comments on the 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Revista Española de Cardiología. 2016;**69**:102-108. DOI: 10.1016/j.rec.2015.11.030

[29] Mehra MR, Kobashigawa J, Starling R, et al. Listing criteria for heart transplantation: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates, 2006. Journal of Heart Lung Transplant. 2006;**25**:1024-1042. DOI: 10.1016/j.healun.2006.06.008

[30] Crespo-Leiro MG, Almenar-Bonet L, Alonso-Pulpon L, et al. Conferencia de consenso de los grupos españoles de trasplante cardiaco. Revista Española de Cardiología. 2007;**7**:4B-54B. DOI: 10.1016/S1131-3587(07)75240-8

[31] Pons J, Leblanc MH, Bernier M, et al. Effects of chronic sildenafil use on pulmonary hemodynamics and clinical outcomes in heart transplantation. The Journal of Heart and Lung Transplantation. 2012;**31**:1281-1287. DOI: 10.1016/j.healun.2012.09.009

[32] Tedford RJ, Hemnes AR, Russell SD, et al. PDE5A inhibitor treatment of persistent pulmonary hypertension after mechanical circulatory support. Circulation. Heart Failure. 2008;**1**:213-219. DOI: 10.1161/CIRCHEARTFAILURE.108.796789

[33] Stehlik J, Edwards LB, Kucheryavaya AY, et al. The registry of the International Society for Heart and Lung Transplantation: Twenty-eighth adult heart transplant report—2011. The Journal of Heart and Lung Transplantation. 2011;**30**:1078-1094. DOI: 10.1016/j.healun.2011.08.003

[34] Barge-Caballero E, Almenar-Bonet L, González-Vílchez F, et al. Clinical outcomes of temporary mechanical circulatory support as a direct bridge to heart transplantation: A nationwide Spanish registry. European Journal of Heart Failure. 2018;**20**(1):178-186. DOI: 10.1002/EJHF.956

[35] Mancini D, Colombo PC. Left ventricular assist devices: A rapidly evolving alternative to transplant. Journal of the American College of Cardiology. 2015;**65**:2542-2555. DOI: 10.1016/j.jacc.2015.04.039

[36] Estep JD, Starling RC, Hormanshof DA, et al. Risk assessment and comparative effectiveness of left ventricular assist device and medical management in ambulatory heart failure patients: Results from the ROADMAP study. Journal of the American College of Cardiology. 2015;**66**:1747-1761. DOI: 10.1016/j.jacc.2015.07.075

[37] Slaughter MS, Rogers JG, Milano CA, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. The New England Journal of Medicine. 2009;**361**:2241-2251. DOI: 10.1056/NEJMoa0909938

[38] Cowger J, Sundareswaran K, Rogers JG, et al. Predicting survival in patients receiving continuous flow left ventricular assist devices: the HeartMate II risk score. Journal of the American College of Cardiology. 2013;**61**:313-321. DOI: 10.1016/j.jacc.2012.09.055

[39] Fitzpatrick JR 3rd, Frederick JR, Hsu VM, et al. Risk score derived from pre-operative data analysis predicts the need for biventricular mechanical circulatory support. The Journal of Heart and Lung Transplantation 2008;**27**:1286-1292. DOI: 10.1016/j.healun.2008.09.006

[40] Kormos RL, Teuteberg JJ, Pagani FD, et al. Right ventricular failure in patients with the HeartMate II continuous-flow left ventricular assist device: Incidence, risk factors, and effect on outcomes. The Journal of Thoracic and Cardiovascular Surgery. 2010;**139**:1316-1324. DOI: 10.1016/j.jtcvs.2009.11.020

[41] Puwanant S, Hamilton KK, Klodell CT, et al. Tricuspid annular motion as a predictor of severe right ventricular failure after left ventricular assist device implantation. The Journal of Heart and Lung Transplantation. 2008;**27**:1102-1107. DOI: 10.1016/j.healun.2008.07.022

[42] Vivo RP, Cordero-Reyes AM, Qamar U, et al. Increased right to left ventricle diameter ratio is a strong predictor of right ventricular failure after left ventricular assist device. The Journal of Heart and Lung Transplantation. 2013;**32**:792-799. DOI: 10.1016/j.healun.2013.05.016

[43] Potapov E, Stepanenko A, Dandel M, et al. Tricuspid in competence and geometry of the right ventricle as predictor so fright ventricular function after implantation of a left ventricular assist device. The Journal of Heart and Lung Transplantation. 2008;**27**:1275-1281. DOI: 10.1016/j.healun.2008.08.012

[44] Cameli M, Lisi M, Righini FM, et al. Speckle tracking echocardiography as a new technique to evaluate right ventricular function in patients with left ventricular assist device therapy. The Journal of Heart and Lung Transplantation. 2013;**32**:424-430. DOI: 10.1016/j.healun.2012.12.010

[45] Arabía FA et al. Biventricular support with intracorporeal continuous flow centrifugal ventricular assist devices. The Annals of Thoracic Surgery. 2018;**105**(2):548-555. DOI: 10.1016/j.athoracsur.2017.08.019

[46] Yancy CW, Jessup M, Bozkurt B. 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology. 2013 Oct 15;**62**(16):e147-e239. DOI: 0.1016/j.jacc.2013.05.019. Epub 2013 Jun 5

[47] Kittleson M, Kobashigawa JA. Cardiac transplantation: Current outcomes and contemporary controversies. JACC Heart Fail. 2017;**5**:857-868. DOI: 10.1016/j.jchf.2017.08.021

[48] Uriel N, Jorde UP, Cotarlan V, et al. Heart transplantation in human immunodeficiency virus-positive patients. The Journal of Heart and Lung Transplantation. 2009;**28**:667-669. DOI: 10.1016/J.HEALUN.2009.04.005

[49] Patlolla V, Mogulla V, DeNofrio D, et al. Outcomes in patients with symptomatic cerebrovascular disease undergoing heart transplantation. Journal of the American College of Cardiology. 2011;**58**:1036-1041. DOI: 10.1016/j.jacc.2011.04.038

[50] Clegg A, Young J, Iliffe S, et al. Frailty in elderly people. Lancet. 2013;**381**:752-762. DOI: 10.1016/S0140-6736(12)62167-9

[51] Sánchez-Enrique C, Jorde UP, González-Costello J. Heart transplant and mechanical circulatory support in patients with advanced heart failure. Revista Española de Cardiología. 2017;**70**:371-381. DOI: 10.1016/j.rec2016.12.036

[52] González-Vílchez F, Gómez-Bueno M, Almenar-Bonet L, et al. Registro español de trasplante cardiaco. XXVIII Informe Oficial de la Sección de Insuficiencia Cardiaca de la Sociedad Española de Cardiología (1984-2016). In: Revista Española de Cardiología. 2017;**70**(12):1098-1109. DOI: 10.106/j.recesp.2017.07.032

[53] Barge-Caballero E, González-Vílchez F, Farrero-Torres M, Segovia-Cubero J. Selección de lo mejor del año 2017 en trasplante cardiaco y asistencia ventricular. Revista Española de Cardiología. 2018;**71**(4):300-301. DOI: 10.1016/j.recesp.2017.10.011

IntechOpen