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Review Article

# Current indications for heart transplantation and left ventricular assist device: A practical point of view

Enrico Ammirati [a,b,*], Fabrizio Oliva [a], Aldo Cannata [a], Rachele Contri [b], Tiziano Colombo [a], Luigi Martinelli [a], Maria Frigerio [a,**]

[a] Cardio-thoracic and Vascular Department, Niguarda Ca' Granda Hospital, Milan, Italy
[b] San Raffaele Hospital and Vita-Salute University, Milan, Italy

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ABSTRACT

Heart transplantation (HTx) is considered the "gold standard" therapy of refractory heart failure (HF), but it is accessible only to few patients because of the paucity of suitable heart donors. On the other hand, left ventricular assist devices (LVADs) have proven to be effective in improving survival and quality of life in patients with refractory HF. The challenge encountered by multidisciplinary teams in dealing with advanced HF lies in identifying patients who could benefit more from HTx as compared to LVAD implantation and the appropriate timing. The decision-making is based on clinical parameters, imaging-based data and risk scores. Current outcome of HF patients supported by LVAD (2-year survival around 70%) is rapidly improving and leads the way to a new therapeutic strategy. Patients who have a low likelihood to gain access to the heart graft pool could benefit more from LVAD implantation (defined as bridge to transplantation indication) than from remaining on HTx waiting list with the likely risk of clinical deterioration or removal from the list because patients are no longer suitable for transplantation. LVAD has also demonstrated to be effective in patients who are not considered eligible candidates for HTx with a destination therapy indication. HTx should be reserved to those patients for whom the maximum clinical benefit can be expected, such as young patients with no comorbidities. Here we discuss the current listing criteria for HTx and indications to implant of LVAD for patients with refractory acute and chronic HF based on the guidelines and the practical experience of our center.



## 1. Introduction

Medical therapy, cardiac defibrillators and devices for cardiac resynchronization therapy have been shown to improve the prognosis of patients with left ventricular systolic heart failure (HF) both in Europe and the United States [1,2]. Despite the combined use of the best therapies, HF usually advances progressively and in some cases it becomes unresponsive to conventional treatments to the extent that surgical revascularization [3,4], ventriculoplasty [5] and mitral surgery become worthless or poorly useful [6,7]. Patients with acute HF requiring inotropic therapy have an approximately 6-month mortality of 25% based on clinical trials, and the European and Italian registries on acute HF [8–10]. These data underscore the need for further treatment options for advanced HF capable of improving symptoms, hospitalizations and improving survival.

The clinical profile of a patient with refractory HF often exhibits at least some of the following characteristics despite optimal therapy: (1) severe symptoms (NYHA class III to IV); (2) episodes with clinical signs of fluid retention and/or peripheral hypoperfusion; (3) objective evidence of severe cardiac dysfunction, that can be demonstrated by at least one of the following: left ventricular ejection fraction (LVEF) <30%; restrictive mitral inflow pattern at Doppler-echocardiography; high left and/or right ventricular filling pressures; and elevated B-type natriuretic peptides; (4) evidence of systemic organ injury, in particular renal and hepatic dysfunctions, underlined by an increase in creatinine and bilirubin levels; (5) severe impairment of functional capacity

*Abbreviations:* HF, Heart failure; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; LVAD, left ventricular assist device; HTx, heart transplantation; ISHLT, International Society of Heart and Lung Transplantation; VAD, assist device; BTT, bridge to transplantation; ESC, European Society of Cardiology; Bi-VAD, Biventricular assist device; QoL, quality of life; DT, destination therapy; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; $pVO_2$, peak oxygen consumption; BMI, body mass index; $V_E/VCO_2$, ventilation equivalent for carbon dioxide; HFSS, Heart Failure Survival Score; SHFM, Seattle Heart Failure Model; IABP, intra-aortic balloon pump; BTD, bridge to decision; BTC, bridge to candidacy; BSA, body surface area; TAH, total artificial heart; LVEDD, left ventricular end diastolic diameter; TAPSE, tricuspid annular plane systolic excursion; MELD, Model for End-stage Liver Disease; INR, International Normalized Ratio.

* Correspondence to: E. Ammirati, Cardio-thoracic and Vascular Department, Niguarda Ca' Granda Hospital, Piazza Ospedale Maggiore 3, 20162 Milan, Italy and San Raffaele Hospital and Vita-Salute University, Milan, Italy. Tel.: +39 02644 2569.
** Correspondence to: M. Frigerio, Cardio-thoracic and Vascular Department, Niguarda Ca' Granda Hospital, Piazza Ospedale Maggiore 3, 20162 Milan, Italy. Tel.: +39 02 6664 7791; fax: +39 02 6444 2566.
*E-mail addresses:* enrico.ammirati@ospedaleniguarda.it (E. Ammirati), maria.frigerio@ospedaleniguarda.it (M. Frigerio).

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demonstrated by either inability to exercise, a 6-minute walk test distance <300 m or a peak oxygen uptake <12–14 ml/kg/min; and (6) history of >1 HF hospitalization in the past 6 months [11]. This definition identifies a group of patients with a high risk of clinical events. These patients, with compromised quality of life and poor prognosis, deserve effective therapeutic options and should be considered for left ventricular assist device (LVAD) or heart transplantation (HTx). The correct timing to refer such patients to centers specializing in HTx and LVAD is fundamental for their survival.

## 2. Epidemiological transition

HTx is considered the gold standard for the treatment of refractory HF [11], but it is available only to a minority of patients because of the paucity of heart donors and of the contraindications or risk factors in several patients with HF [12]. Increasing the pool of heart donors by including older donors might reduce the likelihood of HTx success [13]. From the mid '80s until today in our center the age of donors has doubled reaching an average age of 40 years or older, a trend also observed in other Italian and European centers. It is well known that the donor's age is one of the major prognostic determinants in heart transplant patients (the higher the age, the higher the risk at 1-year and long term mortality) [14]. Patients on waiting list for HTx have a waiting list time in Italy of about 2.3 years (estimated from the time lapse between 2006 and 2010; http://www.trapianti.salute.gov.it/) during which they experience progressive clinical deterioration and an annual mortality of 8–10%. Moreover, 10–15% of HTx candidates are withdrawn from the waiting list every year because they are no longer suitable candidates. Statistics from the *Eurotransplant International Foundation* coordinating the transplantation activity in Austria, Belgium, Croatia, Germany, Luxemburg, Holland and Slovenia have shown that the percentage of HTx candidates receiving a graft at the end of every year has decreased from 63% in 2006 to 45% in 2011, thus highlighting that the lack of organs is emerging as the main issue capable of nullifying the clinical benefit of a clinical procedure such as HTx (http://www.eurotransplant.org). The 2013 report of the International Society for Heart and Lung Transplantation (ISHLT) based on data submitted by 407 centers worldwide concerning 103,299 pediatric and adult HTx between 1982 and June 2011 showed that 1-year survival is 81%, and 5-year survival is 69%, with median survival of 11 years for all and 13 years for those surviving the first year (www.ishlt.org/registries) [14].

Mechanical ventricular assist devices (VADs) have shown in the last years to be effective in improving survival and quality of life of patients with refractory HF and could represent a valid alternative to HTx. LVADs are continuous flow devices made of a pump, which unload the left ventricle of the blood by the presence of an inflow cannula and pump it to the aorta through an outflow cannula. LVADs are placed in the anterior mediastinum and are powered through a wire that exits the body usually at the abdomen level and connects to a controller and to an energy source (battery or *control unit* connected to the electricity supply) (Fig. 1). VAD therapy is a strategy approved in patients with refractory HF who become clinically unstable while on a waiting list for HTx as a bridge to transplantation (BTT) indication and recently inserted in the 2012 European Society of Cardiology (ESC) guidelines on acute and chronic HF [7]. The guidelines also recommend the use of Biventricular (Bi)-VAD (devices designed to assist both the right and left ventricles) as BTT therapy in patients with severe biventricular dysfunction or at high risk of developing right ventricular failure after LVAD implantation [7,15,16]. Because of the high biologic cost and the poor quality of life (QoL) of patients on Bi-VAD, this treatment is not commonly used. Continuous-flow LVADs have also demonstrated to improve the prognosis and QoL in patients with advanced HF who are not considered eligible candidates for HTx (destination therapy [DT]) [17,18]. In the United States of America, a higher number of centers as compared to Europe have exploited an early LVAD implantation strategy in patients meeting the criteria to be placed on HTx list [19]. The north American INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) registry, including over 6000 LVAD implantations, has shown a survival rate of 80% at 1 year and 70% at 2 years in patients implanted with continuous flow LVADs between 2006 and 2012 [20]. It must be noticed that most patients from the INTERMACS registry until 2011 had received a VAD as BTT and that an important percentage of these patients (higher than 50% in 2010, around 40% in 2011) has received a heart graft in the year after VAD implantation [20]. From a trial using Thoratec Heart-Mate II continuous-flow LVAD as DT treatment it is known that the current survival at one year is 73% [21]. In another trial using Heartware LVAD as BTT the survival at one year was 85% [22].

The aim of this review is to improve and standardize the referral of potential HTx candidates in order to guarantee equity in the access to a valuable and scarcely available therapy. On the other hand, mechanical VADs, despite its effectivity, are costly and have a heavy impact on patients' everyday life and quality of life due to the complexity of its management. This concept calls for the need of a better knowledge of the indications and outcomes of such therapy. Here we report a detailed analysis of the patients' subpopulations we consider suitable for HTx and LVAD, in the light of the recent changes in the treatment strategies of refractory HF.

## 3. Current indication for HTx

The recent European guidelines on HF consider suitable for HTx patients with a cardiomyopathy in an advanced stage, severe symptoms, unfavorable prognosis, motivated, emotionally stable and considered capable of coping with the complex post-operative period [7,23]. These observations are definitely based on common sense but they do not suffice in clearly identifying the potential HTx candidate [7]. Probably, the most accurate guidelines on HTx eligibility have been published in 2006 by the ISHLT [24].

In ambulatory patients with refractory HF despite optimal medical therapy, a peak oxygen consumption ($pVO_2$) ≤14 ml/kg/min (patients who do not tolerate beta-blockers) on cardiopulmonary test represents a class I (level of evidence B) indication for HTx. In patients on B-blocker therapy, the value below which HTx should be considered is ≤12 ml/kg/min (class IIa, level of evidence B). The cardiopulmonary test should be maximal (respiratory quotient >1.05) and the anaerobic threshold should be reached. In patients younger than 50 years old and in women, the percentage of the predicted peak oxygen consumption should also be used, with a reference threshold value of ≤50% (recommendation IIb, level of evidence B). In obese patients, with a body mass index (BMI) >30 kg/m$^2$, oxygen peak consumption should be referred to the lean body mass (threshold 19 ml/kg/min) (level of evidence C). If the test is submaximal, the slope of the relationship ventilation/exhaled $CO_2$ (ventilation equivalent for carbon dioxide — $V_E/VCO_2$ slope >35) can be applied as the threshold for HTx eligibility [24].

In ambiguous situations (e.g. when the peak oxygen consumption value falls between 12 and 14), a multiparametric score such as the Heart Failure Survival Score (HFSS) is useful in estimating the patient's prognosis and determine the eligibility to HTx [25]. It must be noted, as the guidelines themselves stress, that the peak oxygen consumption cannot be considered as the sole criterion to consider a patient suitable for HTx and that the decision-making should be based on multiple variables [24]. In Table 1 the main contraindications, divided to major and minor, are listed. They are universally recognized, even though differences can arise on the additive effect of multiple minor contraindications, which are reported

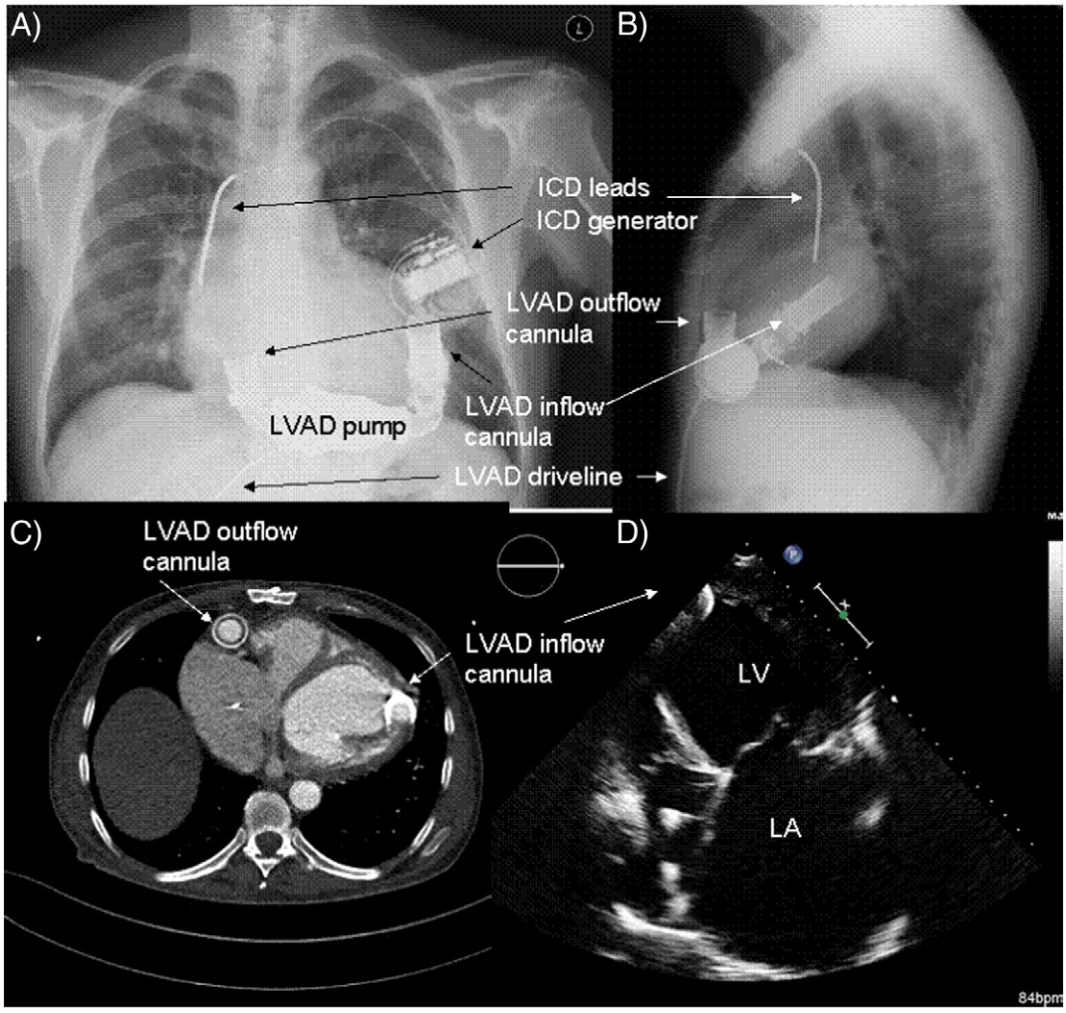


**Fig. 1.** Heart-Mate II model of left ventricular assist device (LVAD) appearance in posterior–anterior (A) and lateral (B) chest X-ray, computerized tomography (C) and ultrasound examination (D). ICD = implantable cardioverter–defibrillator; LV = left ventricle; LA = left atrium.

in the table as "risk factors" [26]. In patients with a history of cancer, the required disease free interval must be at least 5 years long. The presence of pulmonary hypertension with a mean pulmonary pressure higher than 25 mm Hg which is not reversible after drug challenge and a trans-pulmonary gradient (difference between the mean pulmonary pressure and the wedge pressure) higher than

**Table 1**
Main contraindications and risk factors to heart transplant.

| Condition | Contraindication | Risk factor |
|---|---|---|
| Patient's attitude | Refusal of transplant, severe psychosis, recent history of poor compliance, alcohol or recreational drug abuse | Controllable psychiatric disease |
| Malignant neoplasm | Ongoing/recent diagnosis | Previous history, low risk of relapse |
| Pulmonary hypertension | Severe, irreversible | Clinically significant, reversible |
| Major infection | Sepsis, unknown etiology | Identified etiology, responsive to antibiotic treatment |
| Bronchopneumopathy | Severe | Clinically significant |
| Vasculopathy | Severe | Clinically significant |
| Diabetes | Decompensated, complicated | Difficult to compensate |
| Viral hepatitis | Chronic active | HBV-DNA or HCV-RNA positivity with normal liver function |
| Systemic diseases | AL amyloidosis not responsive to treatment | Familial amyloidosis |
| Renal failure | Severe (consider combined transplantation) | Moderate |
| Hepatic damage | Severe | Moderate |
| Obesity | BMI >30 kg/m$^2$ | – |
| Peptic ulcer | Bleeding | – |
| Cholelitiasis | – | Symptomatic (consider surgery before or during HTx) |
| Diverticulosis | Recent diverticulitis, recurrent | Symptomatic |
| Osteoporosis | Severe, debilitating | Symptomatic |
| Pulmonary embolism | Within the past 3 months | – |

**Table 2**
INTERMACS levels — profiles and timing of intervention.

| INTERMACS profiles | Timing of intervention |
|---|---|
| Level 1 — cardiogenic shock | Hours |
| Level 2 — progressive decline despite inotropic support | Days |
| Level 3 — stable, but inotrope dependent | Weeks–few months |
| Level 4 — symptoms at rest | Weeks–few months |
| Level 5 — intolerant to exercise | Variable, dependent on organ dysfunction, nutritional status |
| Level 6 — limitation to exercise | Variable, dependent on organ dysfunction, nutritional status |
| Level 7 — advanced NYHA III | Cardiac transplantation or mechanical hemodynamic support may not be indicated at this time |
| Worsening factors to INTERMACS profiles | |
| Temporary hemodynamic support | Applicable to levels 1, 2 and 3 (hospitalized) |
| Arrhythmias | Applicable to all levels |
| "Frequent flyer" (frequent hospitalizations) | Levels 3 (if not hospitalized), 4, 5, and 6 |

15 mm Hg represents an absolute contraindication to the eligibility to transplantation because of the high risk of right ventricular dysfunction in the post-operative setting. Renal insufficiency can represent a significant risk factor, particularly when the creatinine clearance is <50 ml/min. Even though such threshold is present in the guidelines other factors are also considered in judging the impact of renal failure in specific patients (patient's age, parenchymal renal damage, eligibility to a combined heart–kidney transplantation) [7].

## 4. Revision of the indications to HTx

### *4.1. In-hospital patients with new-onset acute HF or with acute worsening of chronic HF*

The goals of the treatment of acute HF are symptom control, limitation of heart damage (particularly important when at least a partial recovery is foreseeable) and hemodynamic stability in order to guarantee a proper perfusion of peripheral organs in order to prevent multi-organ failure. Advanced HF therapies, which require an intensive care setting and invasive monitoring, include inotropes, vasodilators, and non-invasive and invasive ventilation. When medical therapy does not suffice, in hypotensive patients and in patients with signs of hypoperfusion it is necessary to resort to non-pharmacological therapies such as intra-aortic balloon pump (IABP), which is commonly used in the setting of myocardial ischemia–infarction or acute myocarditis, but also applied in the setting of acute decompensated HF with cardiogenic shock secondary to other causes [7]. For patients with signs of hypoperfusion despite maximal inotropic therapy and IABP, short-term mechanical circulatory assist devices are available. The most utilized circulatory support in the acute setting is veno-arterial extracorporeal membrane oxygenator, capable of supporting both ventricles. Short-term mechanical devices can be used as bridge to decision (BTD) in deteriorating patients before a complete clinical and diagnostic evaluation can be performed (class IIb recommendation, level of evidence C according to ESC guidelines) [7].

We believe that, in the acute HF setting, the following categories of patients should be considered for HTx:

1) Patients with cardiogenic shock in the context of acute myocardial infarction, myocarditis and cardiogenic shock following cardiac surgery (*postcardiotomy shock*). Patients whose circulation is supported through IABP and/or *short-term* mechanical support must have overcome the shock phase and be devoid of signs of overt organ failure in the absence of signs of recovery of heart function. Prompt referral for HTx assessment is warranted when the shift to long-term assist devices in not a feasible option (body surface area, anatomical or socio-cultural issues).
2) *Long-term* VAD patients with acute device dysfunction, device infection or with other device — related complications that cannot be resolved (e.g., through the removal of the infected components, treatment of a bleeding gastro-enteric lesion). It must be mentioned that, in selected cases of device malfunctioning, device replacement is considered.
3) Patients who are being evaluated for or who have already been placed on a HTx list and who deteriorate acutely while having concomitantly a contraindication to risk factors for LVAD implantation (anatomical issues such as small body surface area, mechanical valves, coagulation disorders not allowing antiplatelet/anticoagulation therapy, socio-cultural issues).

The evaluation of these categories of patients and their urgent referral for HTx must follow a multidisciplinary approach (cardiologists, heart surgeons, anesthesiologists, psychologist and other specialists according to the patient's clinical conditions) and must impartially take into account the patient's clinical conditions, heart damage, surgical and post-operative risks and post-transplantation prognosis. Predictive models [27], such as the Seattle Heart Failure Model (SHFM, http://depts.washington.edu/shfm) [28] which has recently been validated in the urgent HTx setting, can be employed as a support to the clinical decision making [29]. Also the INTERMACS classification, which is a scale that correlates the patient's clinical conditions and ongoing pharmacologic support with available devices and timing of intervention (Table 2) [30,31], is frequently used to judge the risk of HTx procedure in urgent conditions. Each nation has its own heart allocation system criteria, which also reflects geographical variability. Italy, the United States and the

**Table 3**
Italian classification for patients referred for heart transplantation in Status 1, 2A and 2B, based upon clinical priority in descending order.

| |
|---|
| Status 1 |
| Patient with totally artificial heart (TAH) |
| Patients with RVAD (*right ventricular assist device*) or bi-ventricular assist device or assisted with extracorporeal circulation or ECMO (*extracorporeal membrane oxygenator*) |
| Patients with LVAD (*left ventricular assist device*) and mechanical support-related complications |
| Patients with IABP (intra-aortic balloon pump) and/or mechanically ventilated |
| Patients not included above, with a life expectancy lower than 7 days |
| Status 2A |
| Patients with LVAD without complications |
| Patients on continuous inotropic support |
| Patients with ICD and malignant relapsing arrhythmias |
| Hyper-immunized patients |
| Status 2B |
| Outpatients not included in the categories listed above |

Eurotransplant Organization apply different organ allocation systems. In Italy, for example, patients on transplantation list are classified as being on Status 1, 2A, 2B according to their priority, and it is feasible for patients on Status 1 or 2A to gain a higher priority as compared to the one established on the basis on geographic and center rotation criteria (Table 3). Moreover, the possibility to advance a heart graft request with "national emergency" priority is contemplated, according to which the first available compatible organ in the whole of the national territory is assigned to the applying center.

### 4.2. Chronic HF HTx candidates

The referral of a patient for HTx and his insertion on a waiting list is a complex process requiring a multidisciplinary approach [26]. The aim of HTx is that of increasing the duration and quality of life. In this regard, the perioperative risk, the quality of the transplanted organ and other organ functions, the risks connected to immunosuppressive therapy and the donor–recipient compatibility must be taken into account [32]. The main challenge for clinicians in the HF field is to recognize those patients for whom HTx is the sole or the best treatment option in terms of risk–benefit ratio. As previously stressed, one of the main criteria for the insertion of a patient on transplantation list is a reduced functional capacity secondary to HF. To this purpose, several scores have been approved: HFSS, validated in the '90s for ambulatory patients with HF, is based on $pVO_2$ and identifies, together with other parameters (hyponatremia, increased heart rate, reduced LVEF, reduced mean blood pressure, ischemic etiology, QRS duration >120 ms), patients with high 1-year mortality. This score identifies patients at low (1-year survival of 89%), intermediate (1-year survival of 72%) and high (1-year survival of 60%) risks [25]. Eventually, another system for prognostic stratification, the SHFM system, was developed which considers biochemical (e.g., total cholesterol, natremia, percentage of lymphocytes, urate level), ongoing medical therapy, and clinical data to identify patients at low, intermediate and high risks [28]. Despite its overall higher complexity, the SHFM system takes into account patient's NYHA class instead of the results of cardiopulmonary exercise testing. Recent data confirm the accuracy of HFSS and SHFM systems in identifying patients at highest short-term mortality risk among those referred to transplantation and those already on transplant waiting list and therefore discriminate patients who would benefit the most from prompt transplantation [33]. Nonetheless, these models do not consider important biochemical variables, i.e. creatinine, liver damage indices (e.g., bilirubin) and natriuretic peptides, which are included in newer acute HF scores [34,35]. Other important clinical parameters, not included in such algorithms but which identify "unstable" patients, are the number of hospitalizations [35], the number of arrhythmic events interrupted by ICD intervention in the previous year and the patient's perception of his clinical condition and its impact on his/her life. Other important variables affecting prognosis and worsening clinical conditions are extra-cardiac comorbidities (e.g. chronic obstructive pulmonary disease, chronic renal failure, insulin-dependent diabetes, colonic diseases), even though these are not generally improved by HTx but, on the contrary, can worsen after transplantation (e.g., diabetes mellitus) and/or increase the likelihood and degree of complications in the post-operative period (e.g., severe chronic obstructive pulmonary disease and infections) [36].

As previously stated, while evaluating a patient to place on a HTx waiting list, an important variable in the decision making process is the presence or absence of pulmonary hypertension. Pulmonary hypertension can be temporally reverted by drugs such as sodium nitroprusside or levosimendan [37]. A net beneficial effect of LVAD therapy even on fixed pulmonary hypertension has been demonstrated [38], On the other hand, a low body weight and an AB blood group are characteristics that can accelerate the patient's access to the pool of donors and therefore they can be taken into account while evaluating a patient for HTx.

To summarize, we can state that, in the setting of chronic HF, the following categories of patients should referred for HTx:

1) Young patients at low surgical risk and at high risk of death or rapid clinical deterioration at short- to mid-term (rapid clinical worsening on optimal medical therapy, frequent hospital admissions for HF, initial and transient organ dysfunctions). This is the group of patients who can benefit the most from HTx.
2) Patients with a low body weight with characteristics, which provide an accelerated access to the pool of grafts.
3) Patients who cannot have access to *long-term* mechanical circulatory assist devices because of morphometric, anatomical or sociocultural issues.
4) Patients refusing long-term mechanical support after being informed of the risk of clinical deterioration while on waiting list.
5) *Long-term* VAD patients with chronic device-related infection or other device — related complications which, cannot be resolved and affect both the quality of life and the prognosis of the patient.
6) Patients with HF secondary to a specific etiology, e.g., transthyretin amyloidosis (where the combined heart–liver transplantation can be indicated) [39] for whom the pathophysiology of the disease itself poses some challenges to the implantation of the currently available mechanical devices; or patients with slowly-progressive muscular dystrophies, whose prognosis is determined by cardiac involvement.

With time, the gap between the numbers of patients listed for transplantation and those who actually receive a heart graft is increasing, particularly among outpatients. This gap, which has led to a mean time on waiting list higher than 2 years in Italy, is going to increase and must be taken into account when referring a patient for HTx. Despite the recipient age limit being 65 years for Europe and 70 years for the United States, the actual trend favors younger patients. The theoretical inclusion and exclusion criteria to place a patient on the transplant list, which have been developed in a time when there was a greater availability of organs, should be revisited and become more restrictive in terms of comorbidities, in order to optimize the outcome of the lower number of transplantation performed today [26].

## 5. Current indication for LVAD in clinical practice

In Table 4 the ESC guidelines on LVAD implantation are listed [7]. The reported cut-off, e.g., an LVEF <25% and a number of hospitalizations equal or greater than 3 per year, must be considered as a guide in the decision making but the final indication to LVAD must be the result of a specialist and multidisciplinary consultation. Our advice to clinical cardiologists is to address patients to LVAD or HTx when his/her clinical conditions are not too advanced because this would increase surgical risk dramatically. Therefore, a prompt referral to centers qualified to

**Table 4**
Indications to LVAD implantation according to the 2012 European guidelines [7].

| |
|---|
| Patients with severe symptoms despite optimal medical therapy and one or more of the following |
| Left ventricular EF <25%, and a $VO_2$ peak <12 ml/kg/min (if measured) |
| ≥3 hospital admissions within the previous 12 months, without evident precipitating factors |
| Dependent on inotropic support |
| Progressive hepatic and/or renal failure secondary to hypoperfusion and to increased left ventricular filling pressure (PWP ≥20 mm Hg, systolic pressure 80–90 mm Hg and cardiac index ≤2 l/min/$m^2$) |
| Initial right ventricular dysfunction |

perform VAD implantation and management of patients with HF who are experiencing a rapid clinical worsening is warranted, since the correct timing can make the difference in terms of outcome [20]. Patient characteristics identifying the population to address to such treatment option include: an age below 70 years, frequent hospitalizations for HF, functional deterioration, and evidence of initial liver or kidney failure (increased bilirubin or creatinine levels) despite optimal medical therapy inclusive of cardiac resynchronization devices, when appropriate. It must be reminded that hospitalizations for HF requiring inotropic therapy identify a population of patients with a worse prognosis on medical therapy as compared to that on LVAD [8]. LVADs can be employed as BTT when it is applied to patients who are already on HTx list with the aim of improving symptoms, reducing hospitalizations for worsening HF and lowering mortality (class I, level of evidence B according to the ESC guidelines) or as DT in patients for whom HTx has been ruled out because they a life expectancy greater than 1 year with the purpose of reducing HF-related hospitalizations and mortality (class IIa, level of evidence B according to the ESC guidelines) [7]. In clinical practice, the timing of implantation is anticipated for DT LVADs as compared to BTT LVADs. Moreover, the timing of implantation of BTT LVAD is anticipated for older patients as compared to young ones, since the latter show a higher likelihood of recovery in the postoperative setting and therefore a higher degree of organ damage is considered acceptable. Because of the paucity of donors and the proven efficacy of LVAD, the distinction between BTT and DT is becoming less evident: in fact, on one hand both BTT and DT can ultimately be considered long-term supports. On the other hand, LVADs can be applied as BTD, i.e. in the evaluation of a patient for HTx by monitoring their response to LVAD therapy, such as in the case of severe pulmonary hypertension (also called bridge to candidacy — BTC). If a patient refers a good QoL after LVAD implantation and is devoid of device-related complications, the option of postponing transplantation might be considered. In fact, redo surgery for HTx represents an adjunctive risk for the patient. On the contrary, there is the case of patients who are not initially considered suitable for HTx because of relative contraindications and/or because of their difficulty to gain access to the pool of donors but who develop LVAD-related complications which ultimately lead them to receive a graft.

Among LVAD-related complications there are: sepsis originating from the skin at the site of exit of the battery wire of the device, episodes of bleeding requiring blood transfusions (mostly secondary to small bowel bleeding) [40], development of right ventricular failure or aortic insufficiency [41], ultimately leading to HF relapse, and ventricular arrhythmias [42]. The inclusion criteria for LVAD are similar to that of HTx, keeping in mind the prognostic factors mentioned previously.

As previously stated, irreversible pulmonary hypertension represents a contraindication to HTx due to unacceptable risk of perioperative right failure, and it becomes a specific indication to LVAD implantation. Contraindications to LVAD implantation, which differ from HTx contraindications, are the low body surface area (BSA), anatomical issues (previous ventriculoplasty, previous mitral and/or aortic valve replacement with a mechanical prosthesis), primary right ventricular dysfunction, restrictive cardiomyopathy, significant ventricular arrhythmic pattern [42,43], coagulopathy (because of the necessity of anticoagulant treatment after LVAD placement) [44], sociocultural issues (inability of the patient to accept and to deal with LVAD management, previous stroke with significant disability), and hemodialysis. In particular, the presence of severe right ventricular dysfunction is a contraindication to LVAD implantation. Despite their technical feasibility in selected cases with biventricular HF, biventricular mechanical assist devices and the total artificial heart (TAH) pose the downside of a higher surgical risk and a worse quality of life. The impact of preexisting right ventricular dysfunction after LVAD implantation is not easy to assess. Right ventricular contractile reserve is usually preserved in patients presenting with high pulmonary pressure values, the exception being excessive right ventricular dilation. Parameters considered predictive of right ventricular dysfunction are [45]: (1) the presence of congestion despite high dose diuretics, (2) the presence of high right atrial pressures despite pulmonary vasodilators and diuretics and other hemodynamic indexes [46], (3) the persistence of liver damage (increased bilirubin levels), and (4) echocardiographic parameters such as an increased right ventricular end diastolic diameter (RVEDD)/left ventricular end diastolic diameter (LVEDD), a reduce tricuspid annular plane systolic excursion (TAPSE), and a reduction in the peak longitudinal strain of the lateral wall of the right ventricle (cut-off value: −9.6%) [47]. It should be remarked that some of the anatomic contraindications such as previous ventriculoplasty, and the presence of a mechanical aortic prosthetic valve need a more complex surgery, and are not absolute contraindications. Patients with a history of cancer, with a negative followup shorter than 5 years, represent another indication for LVAD implantation. These patients might be further considered for a long-term BTC.

Patients older than 65 years and those on HTx list who have a low likelihood of gaining access to the pool of donors (e.g., because of their high BMI) must also be considered. It must be said that surgical mortality and morbidity for LVAD implantation increase significantly above 65 years old. We believe that patients between 65 and 70 years old can be referred for LVAD implantation only in the absence of relevant comorbidities (vasculopathy, renal failure, bowel diseases) and with low score in specific risk algorithms. One of the most recent and applied risk scores is the Model for End-stage Liver Disease score (MELD-UNOS modification) [48] (http://www.mayoclinic.org/medical-professionals/model-end-stage-liver-disease/meld-model-unos-modification) which takes into account 3 laboratory data: International Normalized Ratio (INR), creatinine and bilirubin (once again, stressing the importance of liver and kidney functions in the evaluation of LVAD patients). Lastly, we must be reminded that LVAD is an expensive resource, whose cost can exceed 80 thousand euros, and this consideration must be also part of the decision algorithm. As final consideration, it must be noted that recovery after LVAD implantation, despite described in the literature with a notable frequency [49], is a rare event and most frequently concerns patients with a very recent onset of HF or patients who have undergone coronary revascularization for a recent myocardial infarction [20].

## 6. Conclusions

The present heart graft allocation criteria in several European Countries and in the US define clinical priority according to strict protocols. The allocation system must take into account not only the mortality risk but also the result after transplantation. It has become crucial to allocate the heart graft resource to patients at high risk in order to obtain a prognostic benefit, to those who have no access to other therapeutic options (in particular, *long-term* mechanical supports) and to young patients for whom the expected benefit from HTx in terms of survival and quality of life is considerable (see Fig. 2).

On the other hand, the increasing safety profile of LVAD will lead to a growing application of these devices in patients with HF, also in earlier phases of the disease and mechanical devices might even become a therapeutic resource comparable to dialysis for patients with advanced renal failure.

## Disclosures

None.

## Conflict of interest

None declared.

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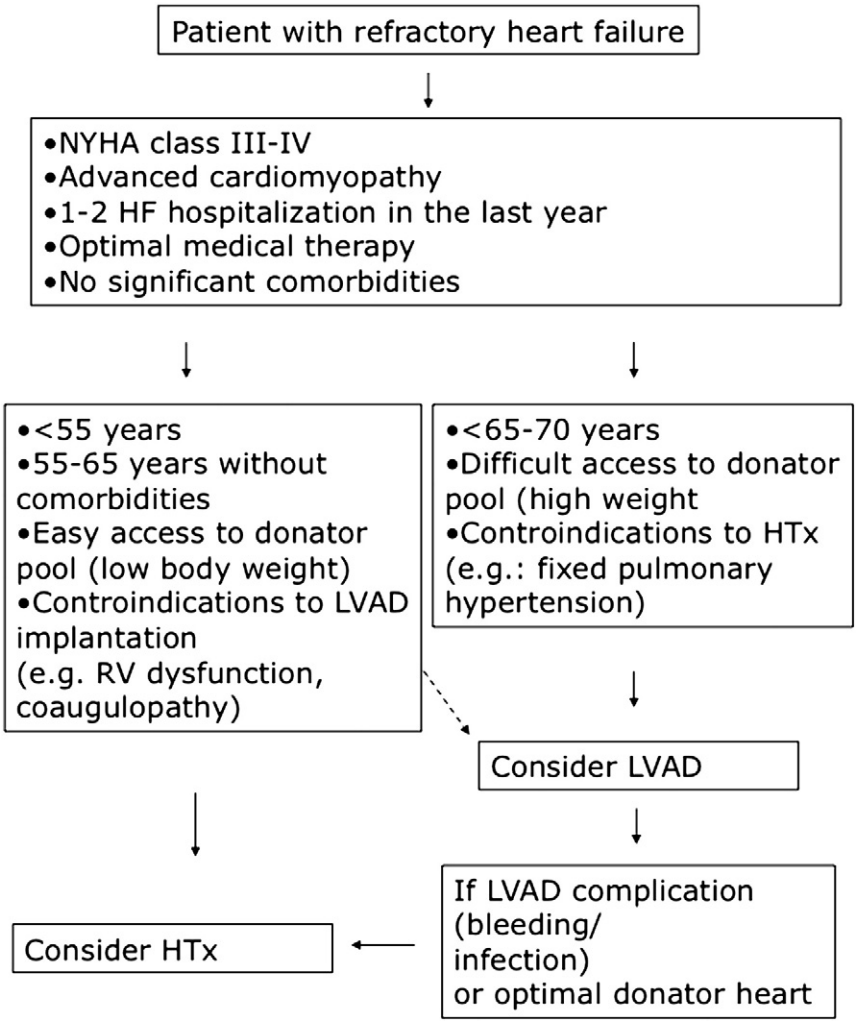


**Fig. 2.** Decision making chart of eligibility to heart transplantation (HTx) and left ventricular assist device (LVAD) in patients with refractory heart failure. NYHA = New York Heart Association.

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