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REVIEW

Patient selection for left ventricular assist devices

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Heart transplantation (HTx) improves symptoms and prolongs life in advanced heart failure (HF), but organ supply is limited. In recent years, mechanical circulatory support and specifically implantable left ventricular assist devices (LVADs) have undergone technical improvements, and outcomes have improved dramatically. Left ventricular assist devices are now viable options for patients with severe HF as bridge to transplantation, destination therapy, or as bridge to recovery. Many believe that LVADs may soon provide outcomes similar to, or better than, HTx, launching a new era of end-stage HF management. The key to improving outcomes is patient selection, but the field is changing rapidly and guidelines and consensus are limited. This review summarizes recent reports of predictors of poor outcomes and provides an overview of selection for LVAD therapy.

Keywords Left ventricular assist device • Mechanical circulatory support • Heart transplantation • Advanced heart failure • Patient selection

Advanced heart failure: scope of the problem

Systolic heart failure (HF) is a growing pandemic with an incidence of 0.15–0.5% and a prevalence of 1–2% in the western world.[1–3] Advanced HF affects 10% of the HF population and is associated with a dismal quality of life, recurrent hospitalizations, and a mortality of up to 50% at 1 year.[1–4] Medical arms in left ventricular assist device (LVAD) trials have generally been inotrope-dependent and have had 1-year mortalities of over 75%.[5,6]

Heart transplantation (HTx) is associated with nearly 90% 1-year survival, 60% 10-year survival, and 95% freedom from symptoms and activity limitations in survivors throughout the follow-up.[7] But because of organ shortage and long waiting times, 10% of transplant listed patients die each year,[8] and many more deteriorate, making transplantation higher risk, and as Eric Rose once stated, 'epidemiologically trivial'. Therefore, recent advances in mechanical circulatory support (MCS), specifically implantable LVAD therapy, are providing alternatives for patients waiting for HTx [bridge to transplantation (BTT)] and also for patients who are ineligible for HTx [destination therapy (DT)] or who are anticipated to experience recovery after left ventricular unloading [bridge to recovery (BTR)].

Left ventricular assist devices

First generation positive displacement pulsatile LVADs best mimic natural conditions but second generation continuous flow pumps have smaller size, simpler implantation, more limited blood contacting area, fewer moving parts and lack valves, air vents and compliance chambers, providing for longer durability with reduced risks for thromboembolism, infection, and malfunction. Third generation devices utilize impeller or centrifugal motors that are mechanically, magnetically, or hydro-suspended. The sophisticated motor and suspension features minimize complications and allow support for many years and potentially decades,[9] further expanding the candidate pool for LVAD therapy.

Current estimates of the number of LVAD candidates range from 10 000[3] to 200 000[10,11] patients in the USA. These patients would benefit both in terms of prolonged survival and improved symptoms and quality of life. Cost-effectiveness is reasonable at US $36 000–86 000 per life year or quality-adjusted life year in broad populations.[12] Left ventricular assist device therapy receives a class IIa level C for BTT and class IIb level C for DT from the ESC[13] and class IIa level B for DT from ACC/AHA.[14]

As technology and long-term outcomes continue to improve, there is indeed potential for LVAD therapy to replace

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transplantation. All patients with New York Heart Association (NYHA) class III–IV/stage D HF are now potential candidates for LVAD support, but risks and benefits will vary considerably between patients. Thus, knowledge among cardiologists and early referral to transplant/LVAD centres are critical. Favourable outcomes require proper patient selection and strategic timing of implantation and an LVAD programme with a multi-disciplinary team of cardiologists, cardiac surgeons, anaesthetists, perfusionists, nurses, social workers, and other professionals with knowledge of the numerous complex patient- and device-specific aspects before, during, and after implantation.

Indications and contraindications for left ventricular assist devices

Cardiac surgeons and HF specialists are continually improving candidate selection for LVAD support. Previously, patients with chronic HF in NYHA class IV and impending cardiogenic shock and/or multi-organ failure[3,15–18] were the main candidates for long-term LVAD. However, with improving device technology, surgical skill, and patient management, we are moving toward implantation in a less ill patient cohort. About 80–90% of LVADs are implanted in transplant candidates who are not expected to survive until transplant or who are deemed too sick for transplant or with potentially reversible transplant contraindications (BTT).[19,20] Destination therapy is for selected patients who are not eligible for HTx, either due to age or comorbidities, for whom pump therapy is meant to be a permanent, life-long, form of left ventricular replacement. The DT population represents a growing share of implants and offers the greatest potential for improvements in HF morbidity and mortality. For some individuals, the candidacy dichotomization is not clear, either for medical or social reasons, and the term 'bridge to decision' has been applied. Finally, BTR is offered for rare patients where LVAD unloading is expected to lead to sufficient reverse remodelling for clinical recovery and the possibility of explantation.

However, the above patient labels are increasingly becoming arbitrary. Up to 17% of DT patients subsequently undergo HTx[4] and many BTT patients subsequently become ineligible for HTx. Recovery is possible but highly unpredictable.[21–24] Some patients have the LVAD explanted despite incomplete recovery because of device-related complications.

The risk prediction tools and criteria for HTx-listing, including the peak VO_2 and the Heart Failure Survival Score (HFSS), are well validated and generally agreed upon.[13,25–27] In contrast, there are no validated selection criteria and indeed no consensus when it comes to candidate selection for LVAD, and selection relies instead on clinical status, inotrope dependence, and invasive haemodynamic parameters.[3,5,6,15–18,28–33] With worsening clinical status, the need for LVAD increases but so does the peri-operative risk, and optimal operative timing becomes difficult (see what follows).

The main goals of LVAD therapy are to improve symptoms, quality of life, and prognosis. But other important goals are to stabilize or reverse organ dysfunction or pulmonary vascular hypertension to increase the likelihood of a successful transplant, to prevent progressive right ventricular dysfunction which would make a future LVAD high risk or contraindicated, or to provide early unloading to prevent remodelling in a cardiomyopathy with hopes for recovery. Expected waiting time for HTx, which are highly variable between different regions and dependent on body size, blood type and panel reactive antibodies, as well as local conditions with regard to types of devices available, practice and expertise, regulation and ethical views also play important roles and make decisions to and timing of implant difficult.[34]

Risks and benefits may be difficult for patients to grasp. Patient preferences are highly variable but in one study LVAD implantation was preferred if life expectancy without LVAD was 6–12 months or less and activity was limited to less than one block walking.[35] This level of severity is similar to that where most clinicians would recommend LVAD implantation (*Table 1*). The urgency of acute implantation and/or bridging from short-term mechanical support often preclude a complete medical and psychosocial assessment, but discontinuation of device support due to undetected conditions is rare and outcomes are similar to elective implantations with complete pre-operative assessments.[36]

An important effort to consolidate experience in the MCS field [left (LVAD), right (RVAD), and bi-ventricular (BiVAD) assist devices and total artificial hearts (TAHs)] is the NIH-sponsored Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS). Currently, 97 sites and 1959 patients are registered.[37,38] European efforts to establish a similar registry are under way. INTERMACS has devised seven levels of severity of HF (*Table 2*).

Table 1 describes these authors' proposed indications and contraindications for LVAD therapy, derived from international consensus and entry criteria in clinical studies.[3,5,6,15–18,28–33,39,40]

Outcomes after left ventricular assist device

Outcomes after LVAD placement are dependent on the era of implant, surgical experience, device and patient characteristics, and time after implant. Operative mortality in well-selected patients has improved to about 5–10%;[30,41] survival to transplant has improved from 33 to 71% in one series;[29] and 1-year overall survival has improved from about 50%[5,6,19] to nearly 80%.[20,28,30,42,43]

The peri-operative period is crucial, with the vast majority of deaths occurring prior to hospital discharge.[4] The most important complications peri-operatively are multi-organ failure, neurologic or peripheral embolic events, bleeding, infection and sepsis, and acute RV failure (see what follows).[44,45] In the longer term, complications include embolic or haemorrhagic stroke, the progression of pre-existing or *de novo* development of RV failure, human leucocyte antigen (HLA) sensitization, renal insufficiency, device failure or infection requiring transplantation, explantation or replacement, gastrointestinal bleeding, and psychological maladjustment.[6,19,28–30,39,45,46] Left ventricular unloading generally improves sustained ventricular arrhythmia burden, but a short-term increase in arrhythmias has been documented.[47,48] Ventricular arrhythmias of up to 12 days have reportedly been tolerated on LVAD support,[49] but decompensation with end-organ dysfunction and syncope are not infrequent.

Three key factors that have contributed to improved patient outcomes include advances in MCS technology, surgical technique and

Table 1 Proposed indications and contraindications for left ventricular assist device

Indications
Strong indication. Bridge to transplant, destination or bridge to recovery. *All* must apply
NYHA IV for 60–90 days
Maximal tolerated medical therapy and CRT/ICD if indicated
Chronic inotrope dependence
LVEF <25%
PCWP ≥20 mm Hg
SBP ≤80–90 mm Hg or CI ≤2 L/min/m^2 or declining renal or RV function[a]
Moderate indication. More often destination than bridge to transplant or recovery.[b] *All* must apply
NYHA IV for 30 days
Maximal tolerated medical therapy and CRT/ICD if indicated
Intermittent inotrope dependence
LVEF <25%
Peak VO_2 <12 mL/kg/min
Indication to enable HTx. *Either* must apply
PVR >5 Woods units, secondary to chronic HF and expected to reverse after LVAD
GFR <25–30 mL/min/1.73 m^2, secondary to chronic HF and likely to improve after LVAD
Conversion from short-term MCS to long-term LVAD
Contraindications
Some may be relative, especially as technology improves.
Acute cardiogenic shock or arrest with uncertain neurologic status[c]
Irreversible contraindication to HTx if destination or recovery is not the aim
Non-systolic HF
Co-existing illness with life expectancy <2 years
Terminal severe comorbidity; e.g. renal disease (haemodialysis or creatinine >2.5–5 mg/dL), metastatic or advanced cancer, severe liver disease (spontaneous INR >2.5, bilirubin >5 mg/dL, or cirrhosis or portal hypertension), severe lung disease (severe obstructive or restrictive disease or home O_2), severe peripheral artery disease, or unresolved stroke or severe neuromuscular disorder
Active uncontrolled systemic infection or significant risk of infection
Active severe bleeding
Chronic platelet count <50 000 × 10^9 per L
Antibody-confirmed heparin induced thrombocytopenia
Right HF not secondary to left HF[a]
Severe RV dysfunction or MOF[a]
Moderate or severe aortic insufficiency that will not be corrected
Mechanical aortic valve that will not be converted to bioprosthesis
LV thrombus that will not be removed
Anatomical considerations such as hypertrophic cardiomyopathy, large ventricular septal defect, or congenital heart disease
Intolerance to the anticoagulant regimen specific to device
Body surface area <1.2–1.5 m^2 or other dimensional or technical limitation
Inability to grasp risks and benefits and provide informed consent
Psychosocial limitations, e.g. inability to comply with medical regimen or device and driveline maintenance or inability of patient or companion to maintain LVAD operation and interpret alarms

NYHA, New York Heart Association; CRT, cardiac resynchronization therapy; ICD, intra-cardiac defibrillator; LVEF, left ventricular ejection fraction; PCWP, pulmonary capillary wedge pressure; SBP, systolic blood pressure; CI, cardiac index; RV, right ventricle; PVR, pulmonary vascular resistance; GFR, glomerular filtration rate; MCS, mechanical circulatory support; MOF, multi-organ failure; HF, heart failure; HTx, heart transplantation; INR, international normalized ratio.

[a]Declining renal function and MOF may make HTx or LVAD higher risk; declining RV function and MOF may make LVAD higher risk and require BiVAD or TAH (see below).

[b]Patients considered for HTx[30] generally require a worse clinical status (haemodynamic derangements) than patients considered for destination therapy.[5] The former group would generally not receive LVAD on a moderate indication since the risks of LVAD outweigh the benefits as HTx before severe deterioration is possible, whereas the latter derive no benefit from deferring LVAD implantation.

[c]These patients may be considered for short-term MCS.

experience, and better patient selection. Modern continuous flow devices[28,30,42,43,46,50] have equal[51] or better survival, less bleeding,[52] infection[52,53] and mechanical failure[54] and shorter duration of intensive care,[51] but possibly more risk of thromboembolism[54] than older pulsatile devices.[5,6,29] One-year survival in subjects undergoing HeartMate XVE (Thoratec Corporation, Pleasanton, CA, USA) implantation for DT in the REMATCH trial was 52%.[5] While the patient cohort was different and interpretation is more difficult

Table 2 INTERMACS levels and outcomes

Level	Description	Number of implants	Number of deaths	Estimated 1-year survival (%)
1	Critical cardiogenic shock	481	121	65
2	Progressive decline	514	102	72
3	Stable but inotrope-dependent	172	20	82
4	Recurrent advanced HF	116	16	75
5	Exertion intolerant	78	16	72
6	Exertion limited	78	16	72
7	Advanced NYHA III	78	16	72
	Overall	1361	275	73

Data includes all types of MCS, including LVAD, RVAD, BiVAD, and TAH.
Implant dates 23 June 2006 to 31 March 2009.
Follow-up presumed until 31 March 2009.
One-year survival is estimated from Kaplan–Meier curves available in reference.[20]
NYHA, New York Heart Association.

because of competing outcomes, in a prospective study of 133 subjects from 26 US centres undergoing HeartMate II implantation as a BTT, survival was 68% at 1 year[30] and when the study was extended to 281 patients, survival was 72% at 18 months,[43] about half of whom were transplanted and half alive on device. Of 571 HeartMate II implants for variable indications from 64 European institutions, 1-year survival was 69%.[42] A clinical trial comparing HeartMate I (VE/XVE) to HeartMate II was recently stopped early because of better outcomes with HeartMate II.[40]

The HeartMate VE or XVE has now been implanted in more than 5000 patients.[55] The importance of experience was illustrated in REMATCH, where patients in the LVAD group enrolled in 1998–99 had 44% 1-year and 21% 2-year survival, respectively, compared with 59 and 38% for those enrolled in 2000–01.[56] In a post-REMATCH DT cohort with HeartMate XVE (Thoratec), 1-year survival was 62%.[57]

Selection and risk scores with focus on overall outcomes

The most important factor for improving patient outcomes after LVAD is careful patient selection. Reviews of patient selection[15,58–61] have generally not included recent risk models[4,62–68] or risk factors.[19,29,69–86]

Patients should be assigned one of the seven INTERMACS levels.[20,61,81] These levels and their corresponding prognosis (*Table 2*) have not been tested or validated in actual patient sets but are helpful for overall clinical assessment. Individual predictors of poor operative outcome include age,[19,29,80,86] female gender,[19] diabetes[19] prior cardiac surgery,[29,70] pre-existing right HF,[80] respiratory failure and septicaemia,[80] pre-operative extracorporeal membrane oxygenation[83] or mechanical ventilation,[19] renal dysfunction,[19,82–85] elevated blood urea nitrogen,[70] coagulopathy and lower platelet and higher white blood cell counts,[19] and worse INTERMACS levels.[20,81]

In addition, there are several risk scores that predict overall outcomes (*Table 3*). The Lietz–Miller destination therapy risk score (DTRS) analysed 45 baseline parameters and outcomes in DT patients in the post-REMATCH era. Laboratory, haemodynamic, and clinical predictors generated a score that divided candidates into low-, medium-, and high-risk strata.[4] Klotz *et al.*[68] analysed 100 pre-operative parameters in a variety of device recipients and found 34 univariate and 13 multi-variate risk factors for intensive care unit mortality. They devised a score with high-, medium-, and low-risk strata. The Columbia University/Cleveland Clinic risk factor selection scale (RFSS)[62] and revised screening scale (RSS)[63] analysed predictors in BTT recipients, and Holman *et al.*[67] in the INTERMACS database.

These studies and risk models have several important limitations. They were derived mainly in patients receiving first generation pulsatile devices; they do not consider under-represented populations such as women, African Americans, and those who due to body size limitations were ineligible for the larger first generation devices. Comorbidities such as diabetes or severe cachexia or obesity were under-represented but have theoretical reasons to fare worse and may preclude transplant. Psychosocial factors and outcomes are not considered. Recidivism of drug and/or alcohol and return to work are unknown. Finally, data are available only on short-term and not longer term outcomes.

Importantly, these models also lack prospective independent validation. We dichotomized 145 LVAD recipients according to published thresholds for several scores and observed hazard ratios for 6-month death, renal failure, and RVAD need ranging from 2.1 to 9.4 when comparing high- to low-risk strata and positive and negative predictive values for death ranging from 23 to 43% and 88 to 91%, respectively.[87] Thus, another major limitation is that while low-risk patients identified by the models are likely low risk, patients with high-risk scores are not necessarily truly high risk. As we move toward less ill patients, these scores will need re-evaluation.

Selection and risk scores with focus on right ventricular failure

In the long term, LV unloading and decreases in LV filling pressures and subsequently pulmonary vascular resistance (PVR) often lead

Table 3 Risk factors for complications or mortality post left ventricular assist device

Study	Columbia University/ Cleveland Clinic risk factor selection scale (RFSS)	P	Columbia University/ Cleveland Clinic revised screening scale (RSS)	P	Lietz–Miller Destination Therapy Risk Score (DTRS)	P	INTERMACS	RR	Muenster	P
Reference	Oz *et al.*[62]		Rao *et al.*[63]		Lietz *et al.*[4]		Holman *et al.*[67]		Klotz *et al.*[68]	
Device	HM IP or HM VE		HM VE		HM XVE		Variable (including 5 RVADs, 77 BiVADs, and 24 TAH)		Variable	
n	56		130		222		420		241	
Risk factors	Urine output < 30 cc/h	3	Mechanical ventilation	4	Platelets count ≤ 148 000/μL	7	Ascites	2.0	Pre-operative transfusions of >10 units RBC and/or >10 units FFP	6
	CVP > 16	2	Post-cardiotomy shock	2	Albumin ≤ 3.3 g/dL	5	INTERMACS level 1	1.6	Inotropes	5
	Mechanical ventilation	2	Pre-operative LVAD	2	INR > 1.1	4	↑ age (60 vs. 50)	1.4	Lactate > 3 mg/dL	5
	PT > 16	2	CVP > 16	1	Vasodilator therapy	4	Bilirubin > 1 mg/dL	1.5	LDH > 500 and/or CK > 200 and/or troponin I > 20 ng/mL	5
	Re-sternotomy	1	PT > 16	1	mPAP ≤ 25	3	BiVAD implant	2.1	C-reactive protein > 8 and/or WBC > 13	4
					AST > 45	2	TAH implant	2.4	Re-sternotomy	4
					Haematocrit ≤ 34%	2			Pre-operative mechanical support	4
					BUN > 51	2			Mechanical ventilation	3
					No inotropes	2			Creatinine > 1.5 mg/dL and/or BUN > 40 and/or CVVH(D)	3
									Emergency implant	3
									Preoperative CPR	2
									Ischaemic aetiology	2
									Heart rate > 100	1
									Platelets < 100 000/μL	1
									Haemoglobin < 12 g/dL and/or haematocrit > 35%	1
									Age > 50	1
Outcome	Score > 5 points → operative mortality 67%		Score > 5 vs. ≤ 5 points → operative mortality 46 vs. 12%		Score and 1-year survival: 0–8 points: 81%, 9–16 points: 62%, 17–19 points: 28%, > 19 points: 11%		RR is for 6-month mortality		Score and ICU mortality: ≤ 15 points: 15.8%, 16–30 points: 48.2%, > 30 points: 65.2%	
Limitations/ comments	Short follow-up; no multivariate analysis; no data on underrepresented populations		Short follow-up; no data on underrepresented populations		No patients with mechanical ventilation, IABP, or BS < 1.7 m^2, no data on underrepresented populations		No data on underrepresented populations		Short follow-up; variable devices; no data on underrepresented populations	

HM IP, HeartMate implantable pneumatic; HM VE, HeartMate vented electric; CVP, central venous pressure (mmHg); PT, prothrombin time (s); *P*, points; HM XVE, HeartMate XVE; RR, relative risk; INR, international normalized ratio; mPAP, mean pulmonary artery pressure (mmHg); AST, aspartate aminotransferase (U/mL); BUN, blood urea nitrogen (U/dL); BiVAD, bi-ventricular assist device; TAH, total artificial heart; RBC, red blood cells; FFP, fresh frozen plasma; LDH, lactate dehydrogenase (U/L); CK, creatine kinase (U/L); WBC, white blood cell count ($\times 10^9$/L); CVVH(D), continuous veno-venous hemo-filtration (dialysis); CPR, cardiopulmonary resuscitation; BSA, body surface area; ICU, intensive care unit.

to improved RV function after LVAD. But in the early post-operative period, numerous complex mechanisms may contribute to RV failure. These include sudden increases in cardiac output, leading to increased venous return and thus RV preload, septal shift causing increased RV wall stress, and increased pulmonary vasoreactivity in the setting of cardiopulmonary bypass, blood transfusions, and inflammation, leading to increased RV afterload.[65]

The incidence of RV failure ranges from 7 to 50% depending on definition and study.[17–19,64–66,69,71,72] Right ventricular failure leads to liver and renal failure, lymphoedema and ascites, and underfilling of the LV and the pump, with potential for arrhythmia and cardiogenic shock. Peri-operative mortality increases from 19 to 43% and survival both to and after HTx becomes worse,[65] although it has been suggested that increased risk is primarily in the peri-operative period and that chronic RV failure post LVAD may not impair successful bridging to transplantation.[88] The impact of long-term LVAD support on RV function and the intrinsic progression of RV cardiomyopathy warrants study and may be an obstacle in the era of 'permanent' LVAD support.

There is limited prospective data but anecdotal evidence suggests that the risk of RV failure can be decreased by pre-operative optimization of nutrition, haemodynamics, and organ function and minimization of RV pre-load, with parenteral nutrition, inotropes, and intra-aortic balloon pump (IABP). Other steps to lower the risk of RV failure include peri-operative minimization of bleeding and transfusion needs, effective coronary perfusion and avoidance of cardioplegia, avoidance of surgical RV injury and RV distension, prophylactic RVAD[89,90] and inotropes, tricuspid annuloplasty, early cessation of positive pressure ventilation and RV afterload reduction with nitric oxide[18,91] nitroprusside, and perhaps prostanoids, endothelin receptor antagonists and phosphodiesterase inhibitors. Nonetheless, escalating inotropic therapy and therapeutic mechanical RV assist often become necessary.

Most important, again, is careful selection. For those accustomed to HTx selection, assessing RV failure risk post LVAD is counterintuitive. A key favourable prognostic factor is the ability of the RV to generate pressure and forward flow; thus high pulmonary artery pressure (PAP) is favourable, whereas high central venous pressure (CVP) and pre-operative RV failure and large tricuspid regurgitation are detrimental. We identified vasopressor requirement, aspartate aminotransferase $\geq$80 IU/L, bilirubin $\geq$ 2.0 mg/dL, and creatinine $\geq$ 2.3 mg/dL as independent predictors or RV failure and constructed an RV failure risk score with an area under the receiver–operating characteristic curve of 0.73.[65] Fitzpatrick *et al.*[64] identified systolic blood pressure $\leq$96 mmHg, cardiac index $\leq$2.2 L/min/m^2, RV stroke work index $\leq$0.25 mmHg L/m^2, creatinine $\geq$1.9 mg/dL, severe pre-operative RV dysfunction and previous cardiac surgery as independent risk factors and constructed an algorithm for predicting RVAD need with >80% sensitivity and specificity. Numerous additional predictors have been identified, many of which directly or indirectly reflect RV function (*Table 4*).[64–66,69,71–73,76,78,79,92] More severe INTERMACS patient profiles more often have biventricular failure and markers of RV failure such as liver dysfunction and ascites, are more likely to require BiVAD or TAH, and have worse outcomes.[81,93] Interpretation of these data is clouded by the fact that most publications identified only univariate predictors and describe exclusively[18,39,69,71–73,76,78,92] or mostly first generation devices.[19,65] Although RV failure appears less common with second generation devices,[28,30] there are also fewer parameters to predict it.[94]

Timing of implantation

With limited data to suggest otherwise, many clinicians implant LV support only when patients are severely ill (*Table 1*). But longer durability and fewer complications with modern devices as well as recognition of the unpredictability of HF deterioration and the importance of being in good clinical and RV status has lead to a shift toward less catastrophically ill patients, such as INTERMACS 3–4 or prior to chronic inotrope dependence. Up to 40% of stable HTx listed patients destabilize to require high-urgency HTx or emergency LVAD.[95] Earlier implantation, before RV and multi-organ failure, leads to better outcomes (see under risk scores above). This is a favoured strategy for DT. Yet, LVADs are still associated with 5–10% peri-operative mortality[30,41] and considerable morbidity and cost, and a HTx-listed patient in good clinical status and a short estimated waiting time may be better served by conservative management.

An emerging issue in BTT patients is whether to implant an LVAD before the institution of chronic inotrope support, a decision that depends on the relative effects of inotropes and LVADs on survival up to and after HTx. Survival on the waiting list depends on the likelihood of being transplanted within a reasonable time.[34] A vast majority of patients implanted to date have been inotrope-dependent.[5,6,17,19,28–30,39,45,46,96] Inotrope dependence is associated with more than 50% mortality at 6 months[97] and the medical arm in REMATCH[5] and INTrEPID[6] had 76 and 89% mortality at 1 year, respectively. However, in HTx-listed patients protected with a defibrillator, inotropes may improve or preserve organ function and clinical status until HTx,[98,99] and pre-HTx inotropes do not impair post-HTx prognosis.[7] A pre-HTx LVAD is associated with the complications of the LVAD itself, may provoke HLA sensitization which can impact heart transplant candidacy, and entails re-sternotomy at the time of HTx. In the ISHLT registry, patients with pre-HTx LVAD fared worse post-HTx.[7] But this registry does not account for selection bias, era of implant, patient characteristics, and other confounding factors. In fact, other studies suggest a neutral[45,100] or favourable[17,29,39,101,102] effect of pre-HTx LVAD on post-HTx outcomes. Furthermore, many patients on inotropes eventually need an LVAD anyway, for successful bridging to transplantation.[103] One attempt at withdrawing inotropes may be attempted,[33] but the need for repeat inotropes should prompt consideration for LVAD implantation. Timing also depends on aim. For inotrope-dependent DT candidates, LVAD implantation should not be deferred, as chronic inotrope use does not prolong survival. It is also important to recognize that poor tolerance of evidence-based pharmacologic therapy, repeat hospitalizations, escalating inotrope, or even pressor needs, or end organ dysfunction, are more important integrated criteria for LVAD than single haemodynamic parameters. Most importantly, outcomes are better for stable patients entering an operative procedure than for subjects who are in extremis.

Table 4 Pre-operative predictors of right ventricular failure after left ventricular assist device implantation

Clinical	Laboratory	Haemodynamic	Echocardiographic
Female gender[64,69,71,76]	High bilirubin,[64,72,92] ***bilirubin ≥ 2.0 mg/dL***[a][65]	**High CVP**[64,66,74,75]	***3-4/4 TR***[66]
Non-ischaemic aetiology[76]	High creatinine,[64,73,78,92] ***creatinine ≥ 2.3 mg/dL***,[65] ***≥1.9***[64]	High **TPG** and PVR[74]	***RV short/long axis >0.6***[66]
Pre-op MCS need[64,65,76]	High AST,[78] ***AST ≥ 80 IU/L***[65]	**High SVR**[66]	***TAPSE < 7.5 mm***[77]
Previous cardiac surgery[64]	High ALT[78]	**SBP ≤ 96** mmHg[64]	**Severe RV dysfunction**[64,65]
Younger age[71]	Low albumin,[64] *albumin ≤ 3.0 mg/dL*[65]	Low RVSWI,[71,75,76] *RVSWI < 450* mmHg L/m^2/beat,[65] ***RVSWI ≤ 250***[64]	High RV wall thickness[73]
Low BSA[64,71,76]	High spontaneous INR[64,66]	Low CI or CO,[65,66,71,92] ***CI ≤ 2.2 L/min/m^2***[64]	Large RVEDV and RVESV[74]
Myocarditis[71]	Low platelet count,[64] *Platelets ≤ 120 × 10^9/L*[65]	Low MBP[64]	
Pulmonary oedema[73]	Elevated white blood cell count,[64] *White blood cells ≥ 12.2 × 10^6/mL*[65]	Low DBP[64]	
Previous TIA/CVA[65]	High BUN,[78] *BUN ≥ 48 mg/dL*[65]	[a]Low sPAP,[64,65,75] [a]high sPAP[77]	
Pre-operative cardiac arrest[65]	Hyperglycaemia[65]	Low mPAP[64,65,71,75,76,78]	
Emergent implantation[92]	High LDH[65]	Low dPAP[75,76]	
Mechanical ventilation[64,65,75,76,78,92]	High C-reactive protein[66]	Low PCWP[92]	
Renal replacement therapy[65]	High NT-proBNP[66]	Low SVO_2[64,73]	
Pre-op IABP need[64,92]		**Vasopressor use**[65]	
Higher revised screening scale,[63] score[75]		[a]Inotrope need increases risk,[66,73] [a]Inotrope use decreases risk[65]	
Higher SAPS II score[66]			

Bold denotes independent predictors of RV failure post-LVAD implantation, generally defined as need for RVAD or prolonged inotropic support. Some studies have identified univariate predictors.[71–73,75,77,78,92] Others have performed multivariate analysis and identified both univariate and independent predictors.[64–66,69,74,76]
Italics denotes specific cut-offs in continuous variables for high risk. Some studies have simply identified significant differences in the variables between RV failure and non-RV failure groups;[69,71–76,78,92] for these, only a qualitative statement ('high' or 'low') is possible. Others have identified specific cut-offs for elevated risk.[64–66,77]
TIA, transient ischaemic attack; CVA, cerebrovascular accident; IABP, intra-aortic balloon pump; SAPS II, New Simplified Acute Physiology Score;[104] BUN, blood urea nitrogen; NT-proBNP, N-terminal pro-brain natriuretic peptide; RVSWI, right ventricular stroke work index = (mPAP − mRAP) × CI × 1000/heart rate; sPAP, systolic pulmonary artery pressure; mPAP, mean pulmonary artery pressure; dPAP, diastolic pulmonary artery pressure; TPG, transpulmonary gradient; PVR, pulmonary vascular resistance; CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure; SVO_2, mixed venous O_2 saturation; CI, cardiac index; CO, cardiac output; SVR, systemic vascular resistance; SBP, systolic BP; MAP, mean BP; DBP, diastolic BP; TR, tricuspid regurgitation; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; RVEDV, RV end-diastolic volume; RVESV, RV end-systolic volume.
[a]Conflicting data in the literature.

Summary

Long-term LVAD therapy is evolving into an effective and reasonably cost-effective therapy for a growing population of patients with advanced HF. Left ventricular assist devices provide dramatic left ventricular unloading and increased cardiac output and improve end-organ function. Left ventricular assist device patients now enjoy a 1-year survival of nearly 80% and reap improvement in symptoms and quality of life from NYHA IV to II.

The most important factor in improving outcomes is proper selection. Selecting patients for LVAD will require a comprehensive assessment of indications and contraindications (*Table 1*), risk factors, and scores for overall outcomes (*Table 3*) and outcomes with regard to RV failure (*Table 4*), as well as optimal timing.

However, LVADs are still associated with an approximately 5–10% peri-operative mortality and frequent short- and long-term complications including right ventricular failure, bleeding, thromboembolic and haemorrhagic stroke, infection, and device failure. Improved technology, experience, and patient selection have improved outcomes, but also make published risk prediction studies obsolete. Thus, more prospective multicentre studies are needed to assess risk in a broad range of subjects undergoing LVAD implantation. Furthermore, as we embark on an era of true long-term support, more studies are needed to predict long-term outcomes.

Conflict of interest: L.J.L. has received speaker's fees from Vingmed, distributor of Thoratec devices. J.M. has received speaker's fees from Thoratec and Terumo corporations. K.A. has received grant support from Terumo and HeartWare corporations. K.A. has a consulting relationship with Thoratec, HeartWare, and Circulite corporations.

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