Advanced heart failure: when and what to consider for left ventricular assist device implantation?

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**Summary**

Survival and quality of life improved significantly with the dramatic changes of heart failure (HF) treatment in the last decades [1]. An unanticipated consequence of this favorable development is the emergence of a patient population increasingly refractory to standard HF treatment. This paradox relates to the fact that none of the currently available drugs or devices completely silences HF disease or protects from the occurrence of new episodes of myocardial damage, the development of cardiorenal syndrom or right heart failure.

**Standard heart failure treatment and advanced heart failure**

Survival and quality of life improved significantly with the dramatic changes of heart failure (HF) treatment in the last decades [5]. An unanticipated consequence of this favorable development is the emergence of a patient population increasingly refractory to standard HF treatment. This paradox relates to the fact that none of the currently available drugs or devices completely silences HF disease or protects from the occurrence of new episodes of myocardial damage, the development of cardiorenal syndrom or right heart failure.

**The prevalence of advanced heart failure**

In the absence of general population-based long-term registries in Switzerland, we can only estimate the number of people suffering from advanced HF. In the European population, the incidence of HF ranges from ≤2 in Italy and Denmark to >6 in Germany (median 3.2 per 1000 person-years) while the prevalence ranges from ≤2 in Greece and Spain to >50 in Lithuania and Germany (median 17.2 cases per 1000 person-years) [2]. Approximately half of the people suffer from HF with reduced left ventricular ejection fraction (=HFrEF; about 100000 persons in Switzerland) and 1–10% of these HF patients (1000–10000 persons in Switzerland) fall into the category of NYHA class 3b/4 (=advanced HF) [1, 3].

**Treatment of advanced heart failure**

Therapeutic options in advanced HF are guidelines-directed medical therapy (GDMT) [4] with positive inotropic drug treatment, MitraClip placement, heart transplantation or assist device implantation in accordance with the individual end-of-life care plan. However, evidence for these treatment options is less strong or currently missing such as for the repetitive application of levosimendan perfusion in the outpatient setting where the ongoing LEODOR trial (NCT03437226) tests the impact of this treatment on outcome [5]. In contrast, a benefit from MitraClip placement can be expected when mitral regurgitation in HFrEF patients remains severe despite of best GDMT and if cardiomyopathy is not too advanced [6]. In any case, heart transplantation (HTx) still remains the “gold-standard” option for eligible patients, although never tested in a randomized clinical trial. But, HTx is limited to 35–50 cases per year in Switzerland, therefore this therapeutic option remains largely reserved for the younger patient without large comorbidity. This makes the case for assist device implantation in the advanced HF patient refractory to GDMT but not eligible or opposed to heart transplantation, all the more, since survival with modern continuous-flow left ventricular assist device (CF-LVAD) treatment has been shown to be superior to medical treatment alone (the ROADMAP-trial; NCT01452802) [39].
Use of assist device treatment in advanced heart failure in Switzerland

In theory, 10–25% of all advanced HF patients should qualify for assist device treatment taking into account limitations related with age, comorbidity or social constraint [7]. In reality, the annual implantation rate is even lower as indicated by a recent report from the United States [8]. On the basis of this report, an annual implantation rate ranging from to 100–250 could be expected in Switzerland while in the annual implantation rate remained limited to 30–40 patients in the last years. This large difference is surprising and we suppose that poor familiarity with the indication for long-term assist device treatment and the clinical profile of a potential candidate may be the reason.

This minireview will therefore focus on indication and comorbidity-associated limitations to this form of advanced HF treatment and the clinical profile of a potential candidate may be the reason.

Indication for assist device treatment

As with other treatments, best selection of the suitable candidate is primordial in assist device treatment [9, 10]. Therefore, the current European Society of Cardiology and European Association of Cardiothoracic Surgery guidelines define the indications for LVAD implantation not only as advanced systolic HF with left ventricular ejection fraction (LVEF) <25% and NYHA functional class IIIb-IV despite optimal treatment. Candidates should likewise present with either high predicted 1-year mortality, dependency on continuous intravenous inotropic support, or fulfill criteria indicating heart transplantation independent whether destination therapy or HTx is the first intention [4, 11] (table 1). These specifications identify potential candidates for assist device implantation, while further stratification of advanced HF into seven different levels has been proven useful for evaluating the urgency of CF-LVAD implantation [12] (for details see table 2). This stratification is nowadays endorsed by the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) and the European Association of Cardio-Thoracic Surgery (EACTS) and was applied for the recruitment of study participants in clinical trials testing the clinical value of CF-LVAD. The majority of these study participants were in INTERMACS levels 1–4, therefore, CF-LVAD implantation in these patients bases on the largest available evidence. While set out on clinically-based subdivision of severity grade in advanced HF, this stratification has already been useful when planted with continuous-flow left ventricular assist device (CF-LVAD) this review will review only discuss indication and limitations related with this form of long-term assist device treatment.

Figure 1: Pros and cons for long-term continuous-flow assist device treatment.

### Table 1: Indications of Mechanical Circulatory Support.

Patients are only to be considered for long-term assist device treatment when reversible causes are ruled out and when cardiac function has not improved with guideline-based optimal treatment.

**Class I recommendation; level of evidence: B**

Advanced HF patients should present with a low left ventricular ejection fraction (LVEF <25%) and persistent NYHA class 3b or 4 despite guidelines-based optimal medical therapy. Furthermore, candidates should present at least one of the following criteria:

1. on inotrope treatment [INTERMACS level 2, 3] (see table 2);
2. recurrent hospitalization for advanced heart failure
3. progressively worsening end-organ dysfunction;
4. peak VO₂ <12 ml/kg/min in cardiopulmonary exercise testing;
5. patients improving on temporary assist device treatment.

**Class Ila recommendation; level of evidence: B**

Assist device implantation can be considered for reversal of elevated pulmonary vascular resistance (bridge to candidacy for possible future HTx) or recovery from transplant contraindication such as obesity, recent cancer, or drug dependency in the context of a heart transplantation project.

**Class IIb recommendation; level of evidence: B**
revealing that INTERMACS level 1 is associated with significantly worse outcome with long-term CF-LVAD treatment when compared to other INTERMACS levels. In consistency with this finding, patients with INTERMACS level 1 are nowadays often bridged with temporary devices towards candidacy to long-term assist device implantation [11].

**Assist device treatment as bridge to transplant versus destination therapy**

For the moment, assist device treatment in Switzerland is largely reserved for heart transplant candidates worsening their clinical condition towards INTERMACS level 2–4 while on the waiting list. However, the worldwide largest growth in left ventricular assist-device volume in the last years has been seen in those patients not considered candidates for HTx. Registry data indicate a higher mortality in the latter patients related to the higher prevalence of comorbidity [13]. This observation was confirmed in the prospective MOMENTUM III trial showing that bridge-to-transplant (BTT) vs destination therapy (DT) with a HM3 device (197 vs 317 patients) have a higher 1- and 2-years survival (88.8 vs 81.5%; 76.8 vs 73.2%, respectively) [14]. Similar survival data were reported from one Swiss CF-LVAD cohorts including BTT and DT patients where 1- and 2-years mortality was 88.4% and 84.4% at 1 and 2 years in the larger cohort (n = 39) [15] while a DT-cohort reported 87.5 and 70% survival (n = 16) [16].

**Patient characteristics associated with a high risk for poor outcome post left-ventricular assist device implantation**

**Age**

While there is consensus in Switzerland that HTx should be limited to advanced heart failure patients £70 years of age, there is no strict age limit for LVAD implantation. Data from the mechanical circulatory support (MCS) Research Network show that 14% of LVAD patients are >70 years. Their unadjusted survival was 75% at 1-year and 65% at 2-years while being 84% and 73% in younger patients [17]. However, survival was not different between age groups when renal function was normal in the elder CF-LVAD patients suggesting that long-term benefit is possible even in this age group [18].

*Indication: class IIa; level of evidence: C*

**BMI**

As with age, there is no cutoff of BMI above which LVAD implantation is contraindicated. In fact, survival after LVAD implant is not different in obese when compared with non-obese patients while HF readmission is more frequent in the former [19]. Since HTx is limited to patients with a BMI <35, CF-LVAD implantation can be applied as a bridge to candidacy strategy enabling recovery from obesity in the otherwise eligible HTx candidate [20]. However, this large effort justifies only when dietary efforts fail and severity of cardiac dysfunction does not permit direct progress towards bariatric surgery.

*Indication: IIa; level of evidence: B*

**Frailty**

Frailty is a biological syndrome of cardiac or extracardiac origin which is associated with decreased physiological reserve. Its diagnosis bases on the presence of unintentional non-edematous weight loss (5 kg in £1 year), self-reported exhaustion, weakness (typically measured as grip strength), slow gait and low physical activity. For the assessment of the nutritional status the serum pre-albumin and total lymphocyte count was shown to be useful for pre-implant identification of high-risk candidates [21]. Furthermore, frailty resulting from cancer, lung disease, cirrhosis, liver disease, peripheral vascular or neurological disease is associat-

### Table 2: INTERMACS classification.

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
<th>time to definite VAD implant</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>“crashing and burning” critical cardiogenic shock</td>
<td>within hours</td>
</tr>
<tr>
<td>2</td>
<td>“sliding on inotropes” declining function despite intravenous inotropic support</td>
<td>within few days</td>
</tr>
<tr>
<td>3</td>
<td>“dependent stability” describes clinical stability with mild to moderate dose of intravenous inotropes or patients on temporary circulatory support without inotropes</td>
<td>within a few weeks</td>
</tr>
<tr>
<td>4</td>
<td>“resting symptoms” “recurrent” rather than “refractory” decompensation</td>
<td>within a few months</td>
</tr>
<tr>
<td>5</td>
<td>“exertion intolerant” describes patients comfortable at rest but intolerant to exercise</td>
<td>variable urgency</td>
</tr>
<tr>
<td>6</td>
<td>“exertion limited” describes a patient able to do mild activity but presentation of fatigue within a few minutes or any meaningful physical activity</td>
<td>variable urgency</td>
</tr>
<tr>
<td>7</td>
<td>“advanced nyha 3” – patients who are clinically stable within a variable reasonable level of comfortable activity with more distant decompensation</td>
<td>variable urgency</td>
</tr>
</tbody>
</table>

For more detailed information see reference 12.
Peripheral vascular disease

The EACTS consensus document on long-term mechanical support points out that peripheral vascular disease does not necessarily argues against CF-LVAD therapy but affords careful evaluation [11].

**Indication:** class I; **level of evidence:** B

Renal dysfunction

Renal dysfunction is a predictor of mortality in HF and after assist device implantation [23]. Impaired renal function is common in patients with advanced HF and is likely to improve when due to low cardiac output or elevated right atrial filling pressures. In contrast, structural kidney disease from co-morbid diabetes or hypertension may not improve while there is hope that CF-LVAD-related increase of renal perfusion may slow progression of kidney disease. In any case, improvement of kidney function by optimal circulatory volume management should be attempted if there is time before CF-LVAD implantation and may provide an additional argument to proceed towards CF-LVAD implantation [24, 25]. However, assessment of the recovery potential of renal function affords in rare case application of percutaneous devices for testing the effect of renal perfusion increase [26].

**Indication:** I; **level of evidence:** B

CF-LVAD implantation might be nonetheless considered in patients with chronic dialysis but is not encouraged because of the significantly increased risk of right ventricular failure [25].

**Indication:** IIIb; **level of evidence:** C

Diabetes

It is recommended to screen candidates before CF-LVAD implant for diabetes mellitus and diabetes mellitus-related end-organ damage (**Indication class I; level of evidence C**). Severe end-organ damage related with diabetes-mellitus is a contraindication to long-term assist CF-LVAD implantation. (**Indication III; level of evidence C**).

Of note, restoration of normal cardiac output after CF-LVAD implant can improve glycemic control in patients with advanced HF [27].

**Respiratory considerations**

Patients with more severe obstructive or restrictive lung disease should be not be considered for CF-LVAD implantation because of the likelihood of worsening pulmonary disease [28]. Therefore, preoperative spirometry and thoracic imaging are recommended before proceeding towards CF-LVAD implantation (**Indication class IIa; level of evidence C**).

**Right ventricular function**

The status of the right ventricle (RV) before CF-LVAD implantation plays an important role because thereafter also venous blood flow increases resulting in a significant increase of RV preload. Furthermore, CF-LVAD related unloading of the LV induces a leftward septal shift which increases the end-diastolic RV volume, changes its geometry, and ultimately can compromise RV function. These postoperative changes occur independent of the preexisting RV function but impact more importantly when RV dysfunction preexists. This can explain why the latter CF-LVAD patients show a higher incidence of postoperative bleeding, renal insufficiency, and prolonged length of hospital stay after CF-LVAD implantation [26]. Preoperative identification of patients at high risk of postoperative RV failure is therefore essential. Advanced echocardiographic evaluation of the RV is an important part of the preoperative evaluation (**Indication class IIa; level of evidence C**), however, there is no consensus on any echocardiographic measure of RV function constituting an absolute contraindication to CF-LVAD implantation [7]. But, preoperatively elevated central venous pressure (CVP) or CVP/PCWP ratio, severe renal dysfunction, and ventilator dependence are fairly consistent predictors of severe right ventricular failure after CF-LVAD implantation [7].

**Arrythmia**

Ventricular tachyarrhythmia (VT) may improve after CF-LVAD implantation but it may *per se* also cause VT. VT or ventricular fibrillation (VF) may be tolerated quite well by some CF-LVAD recipients but will always reduce the flow-output by more than 30% as shown in the LoCo VT study [29]. Successful ICD therapy for VT or VF rapidly restores a normal CF-LVAD flow output arguing in favor of ICD implantation in CF-LVAD patients. However, the actual consensus guidelines of the EACTS nonetheless do not recommend ICD implantation for primary prevention in the immediate interval before planned CF-LVAD implantation (**Indication: class II, level of evidence C**) [11]. This may relate to the fact that a short time interval between ICD and CF-LVAD implantation risks intraoperative lead displacement. However, ESC HF guidelines recommend clearly that patients with advanced HF who are candidates for CF-LVAD implantation should benefit from ICD-implantation for
primary prevention [4]. At our center LVAD candidates are implanted with an ICD device postoperatively if not implanted before CF-LVAD implantation. However, this implantation affords preparatory discussion and patient consent acknowledging the fact that defibrillator may apply a shock while the patient is conscious.

**Hemostatic deficiency and coagulopathy**

Long-term assist device implantation may be considered in candidates with hemostatic deficiency and coagulopathy. *(Indication: IIb; level of evidence: B)* In fact, careful intra- and post-operative management manages the bleeding risk during this period (30), however, hemostasis will be more difficult thereafter because of the fragmentation of the von Willebrand factor by device-related shear stress. This fragmentation results in partial loss of its hemostatic activity mandating careful evaluation of the individual bleeding risk. In this context it is noteworthy that implantation of the HeartMate 3 CF-LVAD is associated with greater preservation of the macromolecular structure of the von Willebrand factor [31] suggesting that the incidence of bleeding may be lower after HeartMate 3 implantation.

**Patients with well-controlled HIV infection, Hepatitis B, or Hepatitis C**

Advanced HF patients with controlled HIV viremia on highly active anti-retroviral therapy can be considered candidates for HTx [32]. With the ongoing organ shortage in Switzerland, implantation of a CF-LVAD in advanced HF patients with HIV represents a viable option. In accordance, today’s antiviral treatment options for hepatitis B or C likewise permit consideration of such patients for long-term assist device treatment, all the more since favorable outcome has been reported [33]. *(Indication: IIa; level of evidence: B)*

**Psychosocial aspects**

Patients undergoing CF-LVAD implantation should be motivated and compliant. Alcohol or drug abuse contraindicate long-term assist device treatment. *(Indication: Class III; level of evidence C)* Patients living alone may do well with a long-term CF-LVAD treatment, however, social network and marital status [34] are relevant for good outcome with LVAD treatment. *(Indication Class IIa; level of evidence B)* Depression and dementia are very common in advanced HF [35] and while depression typically improves after assist device implant [35] *(Indication: IIa; level of evidence: C)* there is concern for dementia *(Indication class: III; level of evidence: C).*

**Valvular disease**

Aortic valve regurgitation affords careful evaluation since >mild aortic regurgitation mandates biological valve replacement *(Indication class Ila; level of evidence B)* or application of a central leaflet coaptation stitch *(Indication class IIB; level of evidence B).* This recommendation is related to the risk that increase of the severity of aortic regurgitation may result in a circulatory short-circuit between the CF-LVAD, the ascending aorta and the left ventricle. A functional aortic bioprosthesis can remain in place *(Indication class I; level of evidence C)* while a mechanic aortic prosthesis should be replaced *(Indication class I; level of evidence C).* An aneurysm of the ascending aorta should be surgically corrected at the time of LVAD implantation. *(Indication class IIa; evidence C).*

The rare cases of concomitant moderate to severe mitral stenosis should be taken care when the CF-LVAD is implanted *(Indication class I; level of evidence C)*; patients with MitraClip placement have to be thoroughly evaluated for mitral valve stenosis *(Indication class I; level of evidence C).* Exchange of functional or biological mitral prosthesis is not recommended *(Indication class III, Level of evidence C).* Correction of the very rare case tricuspid valve stenosis is recommended at the time of CF-LVAD implantation *(Indication class I; level of evidence C).* Repair of moderate to severe tricuspid valve regurgitation may be considered in carefully selected patients at CF-LVAD implantation *(Indication IIB; level of evidence C).* However, any cardiac surgery in addition to CF-LVAD implantation prolongs extracorporeal circulation time, which in turn increases the risk for post-operative right ventricular dysfunction.

**Unexplained anemia or gastrointestinal bleeding**

Gastrointestinal bleeding is a common adverse event after CF-LVAD implantation, however, only 12% of these patients have a history of prior episodes of gastrointestinal bleeding. In contrast, 39% of these patients present RV dysfunction [36] suggesting interplay between RV dysfunction, increase of venous return after CF-LVAD implantation and anticoagulation. In this context, the disappearance of bleeding after HTx provides a further argument in favor of a causative role of the CF-LVAD. Fortunately, digoxin treatment decreases the gastrointestinal bleeding risk suggesting helpfulness of this treatment [37, 38]. Nevertheless, unexplained anemia before CF-LVAD implant should entail extensive work-up searching for gastrointestinal lesions why may bleed with anticoagulation.
Intracardiac thrombi and shunts
Intracardiac thrombi do not represent a contraindication to CF-LVAD implantation but afford full extracorporeal cardiocirculatory support for removal of thrombi in the left ventricle. In contrast, left atrial thrombi with localization in the left atrial appendix can be handled by occlusion of the orifice of the left atrial appendix via epicardial approach using suture or dedicated left atrial appendage exclusion devices (Atriclip Flex.V, Atricure Inc.). Closure of interatrial communications (atrial septal defect or PFO) is mandatory in order to avoid postoperative right to left shunting. This requires extracorporeal cardiocirculatory support and can be achieved using either direct suture or patch closure through a small right atriotomy. If a patent oval foramen is detected only postoperatively, an occluder can be placed using a percutaneous approach.

Absolute contraindications
Active systemic bacterial/fungal infection, irreversible liver dysfunction, poor neurological and cognitive function, dementia, ongoing cancer disease, or active substance abuse with the patient not willing to cease represent absolute contraindication.

Indication class III; level of evidence: C

Summary:
1. Implantation of a CF-LVAD has become a viable option for long-term treatment of patients suffering from advanced HF.
2. Evaluation of CF-LVAD candidacy should therefore pay careful attention to comorbid condition which may improve after CF-LVAD implantation but also has the potential to threaten the long-term benefit.
3. In any case, close collaboration between the CF-LVAD patient, the treating physician and the advanced HF specialist are cornerstone for the maintained success of this life-saving therapy in advanced HF.

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References
The full list of references is included in the online version of the article at https://cardiovascmed.ch/article/doi/CVM.2021.w10079.