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Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology

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Advanced heart failure: HFA position statement

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This article updates the Heart Failure Association of the European Society of Cardiology (ESC) 2007 classification of advanced heart failure and describes new diagnostic and treatment options for these patients. Recognizing the patient with advanced heart failure is critical to facilitate timely referral to advanced heart failure centres. Unplanned visits for heart failure decompensation, malignant arrhythmias, co-morbidities, and the 2016 ESC guidelines criteria for the diagnosis of heart failure with preserved ejection fraction are included in this updated definition. Standard treatment is, by definition, insufficient in these patients. Inotropic therapy may be used as a bridge strategy, but it is only a palliative measure when used on its own, because of the lack of outcomes data. Major progress has occurred with short-term mechanical circulatory support devices for immediate management of cardiogenic shock and long-term mechanical circulatory support for either a bridge to transplantation or as destination therapy. Heart transplantation remains the treatment of choice for patients without contraindications. Some patients will not be candidates for advanced heart failure therapies. For these patients, who are often elderly with multiple co-morbidities, management of advanced heart failure to reduce symptoms and improve quality of life should be emphasized. Robust evidence from prospective studies is lacking for most therapies for advanced heart failure. There is an urgent need to develop evidence-based treatment algorithms to prolong life when possible and in accordance with patient

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preferences, increase life quality, and reduce the burden of hospitalization in this vulnerable patient population.

Keywords
Heart failure ● Heart transplantation ● Heart-assist devices ● Extracorporeal membrane oxygenation

Introduction

Although patients with chronic heart failure have improved outcomes with implementation of evidence-based therapies, ultimately, they still progress to an advanced stage of the disease. Patients with advanced heart failure comprise an estimated 1% to 10% of the overall heart failure population,[1–3] and the prevalence is increasing due to the growing number of patients with heart failure and their better treatment and survival. A thorough definition of advanced heart failure is mandatory to facilitate appropriate application of treatment such as heart transplantation or long-term mechanical circulatory support (MCS) devices.

It is often a general cardiologist who is responsible for directing patients to advanced heart failure resources and helping patients navigate next steps in care. Thus, clinicians need to be appropriately equipped to identify patients that might be candidates for advanced heart failure therapies and to recognize the optimal time for referral. Of equal importance, physicians should be prepared to address the needs of patients who are clearly not eligible for advanced heart failure therapies, engage in discussions about changing goals of care, and optimize management strategies to lessen the symptomatic burden of advanced heart failure and improve quality of life.

The management of patients with heart failure to improve their quality of life and longevity is a mission of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). In this context, the HFA has prepared this position document to (i) describe the clinical characteristics of patients with advanced heart failure, (ii) inform physicians about markers of poor prognosis that indicate an advanced stage of disease, (iii) educate physicians on optimal short-term management strategies for these patients in order to improve their candidacy for heart transplantation or MCS, (iv) enable physicians to recognize the optimal time and processes for referring patients to advanced heart failure centres, and (v) ensure collaboration between advanced heart failure, palliative or symptom-focused care including end-of-life care teams. This position statement summarizes the best available evidence, practice standards, and expert opinions on the management of patients with advanced heart failure. This article is intended to guide general cardiologists, heart failure cardiologists and other professionals involved in the care of these patients such as internists, primary care physicians, and nurses through transitions in care.

Definition of advanced heart failure

Prior definitions for patients with advanced heart failure are shown in *Table 1*.[3–6] The criteria suggested in the 2007 HFA position statement identified a stage where conventional treatments (i.e. guideline-directed drugs, devices, conventional surgery) are insufficient to control the patient's symptoms, and advanced therapies (e.g. cardiac transplantation, MCS) or palliative therapies (e.g. inotropic infusions, ultrafiltration or peritoneal dialysis to control volume, or end-of-life comfort care) are needed. Overlapping terminology can be used to describe these patients; for the purpose of this document, we consider 'advanced', 'refractory', and 'end-stage' heart failure interchangeable terms, all reflecting patients who should be evaluated for advanced heart failure therapies. The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles are also useful to further describe clinical parameters and characteristics consistent with a need for advanced therapies (*Table 2*).[7–9] However, it must be noted that the INTERMACS profiles were developed to classify patients to being considered for long-term MCS device implantation based on symptoms and haemodynamic compromise and, more important, is specific for heart failure with reduced ejection fraction (HFrEF), whereas our classification and, in general, the term of advanced heart failure can be applied also to patients with heart failure with preserved ejection fraction (HFpEF).

Limitations of the 2007 Heart Failure Association position statement for advanced chronic heart failure

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Advanced heart failure encompasses patients who remain severely symptomatic despite optimal guideline-directed management regardless of left ventricular ejection fraction (LVEF), including patients with advanced heart failure who remain ambulatory but are essentially New York Heart Association (NYHA) class IV. The first HFA position statement acknowledged the importance of HFpEF and included a provision to diagnose advanced heart failure on the basis of high B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP) levels independently of LVEF values.[4] Despite this recognition, advanced symptoms in the setting of HFpEF were not emphasized sufficiently to meet current clinical practice needs. It is important to raise awareness that advanced heart failure does not depend on ejection fraction, but on the patient's symptoms, prognostic markers, presence of end-organ damage, and goals for therapy.

The treatment armamentarium has improved for HFrEF since the 2007 HFA document, with clearer indications for cardiac resynchronization therapy (CRT) and the availability of new drugs, such as ivabradine and sacubitril/valsartan, although to date, no trial has specifically addressed patients with advanced heart failure. The need to optimize such therapies should be reflected in definitions of advanced heart failure, and patients must be treated according to the best available medical and device therapies (unless contraindicated) before advanced therapies are considered.[9,10]

Further criteria must also be considered. First, outpatient visits with intravenous administration of loop diuretics and/or other vasoactive medications are increasingly replacing hospitalizations for heart failure.[11] Thus, both unplanned outpatient visits and hospitalizations for worsening symptoms of heart failure must be considered amongst criteria for the diagnosis of advanced heart failure to reflect evolving clinical practice. Second, recurrent malignant arrhythmias are now well recognized contributors to and can be consequences of advanced heart failure.[12–14] Third, co-morbidities can complicate the evaluation of patients with advanced heart failure, and sometimes influence candidacy for MCS or heart transplantation, although it should be recognized that in some cases co-morbidities may improve after application of advanced therapies.[15–18] End-organ damage, in particular kidney or liver dysfunction and pulmonary hypertension, may be a consequence of acute congestion and/or low-output state, but it may be difficult to distinguish primary and secondary dysfunction or to predict reversibility.

Updated definition of advanced heart failure

To address these areas, an update to the definition of advanced heart failure is warranted. Our updated criteria for the identification of patients with advanced heart failure are outlined in *Table 3*. Compared with the former HFA definition of advanced heart failure, we have updated the following criteria:

- Criterion 2 is now based completely on the most recent ESC heart failure guidelines.[9] The ESC criteria are sufficient to define cardiac dysfunction, and they can be used for the definition of advanced heart failure when accompanied by other criteria that characterize patient severity. Using the ESC criteria for cardiac dysfunction gives the same importance to all patients with heart failure, independent of LVEF. With a few exceptions, such as patients with hypertrophic cardiomyopathy or restrictive cardiomyopathy,[19] the vast majority of patients with an indication for heart transplantation or MCS have a reduced LVEF. However, at least 50% of patients hospitalized for acute heart failure have a preserved LVEF, and these patients may also be considered advanced provided the other criteria outlined in the definition are present.
- Criterion 3 now includes heart failure hospitalization. Unplanned visits for heart failure have been added and given the same value as a heart failure hospitalization.[20–23] Malignant arrhythmias have been added as a major cause of acute events. Criterion 3 acknowledges that acute events leading to one or more unplanned visit(s) or hospitalization(s) within 12 months are the hallmark of advanced heart failure, independent of treatment, with emphasis placed on the instability of the clinical course and resource utilization.

Prognostic stratification

Accurate prognostication is especially important in advanced heart failure to identify the ideal time for referral to an appropriate centre (i.e. those centres capable of providing advanced heart failure therapies), to properly convey expectations to patients and families, and to plan treatment and follow-up strategies.[24,25] However, detailed prognostication is complex and difficult. It is required for selection for advanced heart failure therapy, but it is not required for referral to an advanced heart failure centre.

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Referral requires only the presence of advanced heart failure. Numerous single risk markers and composite risk scores have been derived, validated, and are available as interactive online tools. These multiparametric scores can assist the heart failure team in arriving at comprehensive risk assessments to inform decisions.[9] However, there are several important considerations and limitations that are often overlooked when applying these tools in clinical settings and in clinical trial design.

First, many prognostic tools were derived and validated in selected clinical trial populations or at single centres and may not be generalizable to 'real-world' heart failure populations or individual patients. Second, most of the available tools for estimating prognosis were not derived from advanced heart failure cohorts. Third, risk markers and scores perform well for mortality but less well for cardiovascular or heart failure specific death or hospitalization.[9,26–28] Fourth, not all risk markers are also risk factors. Thus, targeting a risk marker will not automatically improve outcomes. One example includes pharmacologic interventions targeting haemodynamics, which do not correct the underlying aetiology of heart failure and do not improve outcome, although an impaired haemodynamic profile is a very powerful indicator of poor prognosis. Finally, appropriate clinical use of any prognostic variable (biomarker) or multiparametric score requires understanding of discrimination (between event and non-event), calibration (predicted vs. actual outcome), and reclassification (how well addition of information correctly reclassifies events).[24] For example, NT-proBNP discriminates very well (i.e. higher values accurately predict greater heart failure risk), but it calibrates poorly because there is no particular value of NT-proBNP that corresponds to a particular expected mortality rate or that can be used to list a patient for cardiac transplantation. Finally, it must be kept in mind that different prognostic scores may perform more or less equally in patient cohorts, while providing very different prognostic estimates when applied to individuals.[29]

Nevertheless, objective risk markers and scores, especially as part of a comprehensive assessment performed by the heart failure team, are useful for prognostication, prioritization, and triage for advanced heart failure interventions, including selection for cardiac transplantation.[25] It is useful to consider risk markers from multiple pathophysiological domains (*Table 4*).[8,25,27,28,30–127] Clinical history such as recurrent heart failure hospitalizations, and the physician's impression from the patient encounter are critical. An expanding spectrum of parameters are available from echocardiography and other imaging modalities, and they may serve not only for prognostication but also to guide patient management, gradually taking the place of right heart catheterization, though with some limitations.[128,129] Invasive haemodynamic assessment does not improve the accuracy of heart failure prognostication, but it is a critical component of the work-up for potential heart transplantation or long-term MCS recipients. It allows an accurate estimate of important parameters, such as the pulmonary capillary wedge pressure, pulmonary vascular resistance, transpulmonary gradient, and adds to the assessment of right ventricular function.[25,130,131] Invasive haemodynamic monitoring is not routinely recommended for in-hospital management of patients with advanced heart failure,[132] but it is useful for the evaluation and treatment of patients in critical conditions, e.g. cardiogenic shock, not responding to standard treatment. The cardiopulmonary exercise test (CPET) provides a set of integrated parameters that are impacted by cardiac, pulmonary, peripheral and psychological factors, and it is a critical component of the work-up in patients with advanced heart failure who are able to perform the test. Co-morbidities are common and important prognostic markers in heart failure. In selecting advanced heart failure interventions, physicians should consider both prognosis without therapy (indication) and the potential for adverse outcomes with interventions (contraindications). Contraindications are often related to co-morbidities that cannot be modified by heart failure therapy and predispose patients to adverse outcomes after heart transplantation or MCS. End-organ dysfunction such as chronic kidney disease (CKD) may be intrinsic or secondary to heart failure. Liver dysfunction in the setting of advanced heart failure has been less extensively investigated than renal insufficiency. The most common indices of acute and chronic liver damage due to congestive and/or low-output state are increased transaminase levels (AST, ALT) and increased serum bilirubin, respectively.[16] End-organ damage impacts outcomes, and it is important for the heart failure team to assess whether such damage is likely reversible after transplantation or MCS. Other co-morbidities, such as disordered iron metabolism, must be systematically investigated[9] as treatment may improve quality of life and symptoms.[9]

No single variable can account for all prognostic dimensions. Multivariable prognostic scores outperform individual markers both in terms of discrimination and calibration. Numerous scores have been derived and validated for both acute heart failure and outpatients. Selected prognostic scores for advanced but non-hospitalized heart failure include the Heart Failure Survival Score (HFSS),[133] the Seattle Heart Failure Model (SHFM),[109] the Metabolic Exercise test data combined with Cardiac and Kidney Indexes (MECKI) score,[134–136] and the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC)[105] (*Table 5*). The SHFM has been shown to underestimate the risk of decompensation and

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indication for left ventricular assist device (LVAD) in patients with advanced heart failure.[110,137,138] Therefore, this risk score should be used cautiously in the setting of advanced heart failure.

Although there are no validated studies that indicate which variables and cut-offs can be used as criteria for referral to advanced heart failure centres, the totality of data on heart failure prognostication allows for some suggested clinical, laboratory, and echocardiography criteria that may serve as triggers for referral. These are listed in *Table 6*.

Finally, non-patient-related factors, such as organization of care and access to treatment and follow-up, are also strongly associated with outcomes. Despite the availability of an extensive set of prognostic parameters, predicting outcomes both in the absence and presence of advanced heart failure interventions remains difficult, and patients are often referred to advanced heart failure centres too late. The concept of active screening for advanced intervention has been proposed to improve appropriate referral and treatment in advanced heart failure[139,140] (*Figure 1*).

Exercise testing

Cardiopulmonary exercise testing is reproducible and provides important information about cardiovascular reserve and prognosis. Traditionally, CPET has been part of the evaluation of ambulatory patients with advanced heart failure if they were considered for heart transplantation or long-term MCS. Guidelines for listing elective patients for heart transplantation still state that a peak exercise oxygen consumption (pVO_2) ≤12 mL/kg/min is a potential indication for heart transplantation (≤14 if beta-blocker intolerant).[25] Importantly, confirmation that peak values have been achieved is mandatory, for instance by ensuring a respiratory exchange rate >1.05. In addition to pVO_2, other CPET findings may help inform the evaluation of heart transplantation candidacy. In women or patients <50 years of age, achieving a pVO_2 ≤50% of predicted may be appropriate to determine heart transplant referral.[25] Additionally, patients with a ventilation equivalent of carbon dioxide (V_E/V_{CO2}) slope >35, particularly those with a submaximal CPET, have a poor prognosis, and V_E/V_{CO2} slope may be applied in the patient evaluation.[25] Performing high quality CPET is not a simple task and reliable results require staff skilled in the procedure as well as meticulous interpretation.[141] However, CPET remains highly valuable to identify patients with potential indications for heart transplantation or long-term MCS and should be part of the work-up for elective patients with advanced heart failure in whom these treatments are considered, particularly in those patients reporting a disproportion between symptoms and objective parameters.[142]

The 6-min walk test (6MWT) is easy to perform and widely used in heart failure. It should be emphasized that CPET and 6MWT are very different measures. Peak oxygen uptake during CPET expresses maximal cardiac output and the arteriovenous oxygen difference during maximal exhaustion, while the 6MWT is performed at submaximal exercise levels. Thus, the 6MWT does not accurately reflect functional capacity as assessed by pVO_2,[127] but it is correlated to pVO_2 and predicts survival in heart failure in some,[127] but not all studies.[143–145] The 6MWT has been used as a screening tool in advanced heart failure (<300 m) and also as an endpoint in clinical trials. Use of the 6MWT is encouraged to give objective evidence of functional impairment in patients with advanced heart failure where CPET is not indicated as described above. In addition, the 6MWT can be a useful tool to assess frailty, which represents a significant risk marker and potential contraindication to non-pharmacologic strategies in advanced heart failure.[99,146]

Management strategies for patients with advanced heart failure

Short-term management of advanced heart failure

Advanced heart failure therapies refer to long-term MCS or cardiac transplantation. However, in situations where the patient's clinical condition deteriorates, or end-organ function is compromised, short-term therapies may be needed until MCS can be implanted or while the patient is waiting on the transplant list. Discussion of the patient and overall plan for advanced heart failure therapies with a specialized advanced heart failure centre (i.e. hub centre) can be helpful to select the most appropriate short-term management strategy.

Intravenous vasoactive drugs

It is well known that inotropes may improve haemodynamics and help reverse worsening end-organ

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function in advanced heart failure (*Table 7*). However, inotropes studied in randomized clinical trials have generally not been associated with improved outcomes, and have, in some studies, worsened prognosis.[147–149] Hence, inotropes have no place in the routine treatment of advanced heart failure. However, there is expert opinion that inotropic support may be necessary in refractory heart failure in selected patients as a bridge to temporary MCS, long-term MCS, or heart transplantation. Inotropes may also be used as short-term therapy in patients with low cardiac output and evidence of end-organ dysfunction, for instance during decongestion. Long-term (i.e. months) or chronic treatment after discharge with inotropes for patients waiting for transplantation, is not routinely recommended. These patients should probably be considered for long-term MCS if feasible.[150,151] However, patient preferences regarding inotropic therapy or MCS for patients awaiting transplantation should be assessed. Continuous inotropes may be acceptable as a palliative measure for patients without other advanced treatment options.

Vasopressors (dopamine, norepinephrine, epinephrine) are broadly associated with worse outcomes in observational studies,[152] and low-dose dopamine does not improve congestion or cardiovascular outcomes compared to placebo in acute decompensated heart failure.[153,154] Hence, these agents should be reserved for patients with low systolic blood pressure and evidence of organ hypoperfusion (cardiogenic shock) at the lowest dose that obtains the desired clinical goals, and only if the low blood pressure is considered a reversible condition or definitive therapy (long-term MCS or transplantation) is planned.

Intermittent use of inodilators for long-term symptomatic improvement or palliation has gained popularity, especially use of levosimendan, since the haemodynamic effect may last for >7 days after a 12–24 h infusion because of the pharmacologically active metabolite with a long half-life.[155] While meta-analyses of several heterogeneous small trials of a repeated infusion strategy have suggested a positive effect on survival[156] and a reduction in hospitalizations,[157] such a survival effect has not been demonstrated in a single, adequately sized, prospective study. The LION-HEART pilot study randomized 69 patients with advanced heart failure to placebo or levosimendan 0.2 μg/kg/min over 6 h every 2 weeks for 12 weeks.[158] NT-proBNP over time, the primary endpoint, was significantly lower in the levosimendan group compared to the placebo group. Patients randomized to levosimendan were also less likely to be hospitalized for heart failure or experience a decline in health-related quality of life compared to placebo. Adverse events were similar between groups.[158] More studies are needed to determine if this approach may be useful for patients with contraindications to transplantation or long-term MCS.

Whether or not to implant an implantable cardioverter-defibrillator (ICD) in patients listed for heart transplantation is still a matter of debate. This decision is usually made on an individualized basis, balancing the expected risks of sudden death and device-related complications, and considering the expected waiting time for transplantation. In the absence of randomized trials, the best evidence regarding this controversial topic comes from a Swiss observational study,[159] in which a significant survival benefit was observed for ICD carriers, both as primary or secondary prevention, with a median waiting list time for transplantation of only 8 months. In recent years, wearable defibrillators have emerged as a potential effective and less invasive alternative to conventional implantable devices for this purpose.[160]

Management of congestion

Most of the heart failure hospitalizations are due to signs and symptoms of fluid overload.[161] Recurrent congestion worsens patients' outcomes. Loop diuretics remain the cornerstone for the treatment of congestion in the patients with heart failure. Diuretic therapy is thoroughly described in the current guidelines for heart failure treatment and their further discussion goes beyond the aims of this article. The clinical course of patients with advanced heart failure is often characterized by kidney dysfunction (cardiorenal syndrome) and by diuretic resistance. The first may have multiple mechanisms including abnormal haemodynamics, neurohormonal activation, excessive tubular sodium reabsorption, inflammation, oxidative stress, and nephrotoxic drugs.[161] Loop diuretic resistance is generally due to a series of renal adaptations after diuretic use ('braking phenomenon') including hypertrophy and hyperfunction of other sites of the nephron and to increased renin secretion in the macula densa. Increased uremic anions and proteinuria also impair achievement of therapeutic concentrations at the diuretic's tubular site of action.[161]

Concomitant administration of thiazide diuretics or metolazone with loop diuretics is used to overcome the braking phenomenon. However, no evidence from clinical trials exists to guide this practice. Ultrafiltration (UF) might be an alternative to loop diuretic administration. It removes isotonic fluid

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without direct activation of the renin–angiotensin–aldosterone system, if fluid removal rates do not exceed capillary refill. Greater access to UF stems from the development of simplified devices not requiring specialized technicians or acute care settings.[162]

The adjustment of UF rates to patients' vital signs and renal function may provide more effective decongestion and fewer heart failure events than standard of care.[161] The results of UF studies are summarized in the online supplementary *Table S1*.

Practice guidelines suggest that patients with an inadequate response to oral diuretic treatment should receive intravenous diuretics starting with an intravenous dose greater than that of the oral treatment. The initial dose of the intravenous treatment should be increased in case of an inadequate response.[6,9] Persistent congestion can then be treated by adding thiazide, or thiazide-like, diuretic agents, aldosterone antagonists. Only if these measures fail can UF be considered.[6,9] However, favourable results of trials of early UF underscore the need for additional investigation of UF in clinical settings as an alternative to high-dose diuretic treatment.[163,164]

Once an initial UF rate is chosen, it should be either maintained or reduced because capillary refill from the interstitium decreases as fluid is removed.[165] Rates of UF >250 mL/h are not recommended.[164] Patients with right-sided heart failure or HFpEF are susceptible to intravascular volume depletion and may only tolerate low UF rates (50 to 100 mL/h).[164] Extracorporeal fluid removal is better tolerated when conducted with low UF rates delivered over several hours. Patients' current weight can be compared with that preceding the signs and symptoms of congestion and used as the target for fluid removal.[164] Inline haematocrit sensors permit continuous estimation of blood volume changes during UF and can be programmed to stop fluid removal if the haematocrit exceeds a set threshold (e.g. 5% to 7%) and resume therapy when the haematocrit value falls below the pre-specified level, indicating an adequate intravascular volume. Bioimpedance vector analysis, bioimpedance spectroscopy, electromagnetic technology and pulmonary artery pressure sensors all have limitations for estimation of blood volume and more research in this area is needed.[161]

The Peripheral Ultrafiltration for the Relief from Congestion in Heart Failure (PURE-HF) trial (NCT03161158) will evaluate whether peripheral UF combined with low-dose intravenous diuretics result in fewer heart failure events and cardiovascular deaths at 90 days compared to guideline-directed therapy including intravenous diuretics in patients with heart failure hospitalized for congestion.

Peritoneal dialysis is a home-based therapeutic modality than can be used in patients with refractory heart failure, cardiorenal syndrome and fluid overload. The peritoneum is used as the filter through which solute molecules can be exchanged between the dialysate (delivered to the peritoneal cavity through a catheter) and the blood.[166] With peritoneal dialysis, removal of sodium and water by UF occurs because of the osmotic pressure gradient between the hypertonic dialysate and the hypotonic peritoneal capillary blood. Peritoneal dialysis has a role in patients with concomitant heart failure with and without advanced CKD (Stages IV/V) in whom peritoneal dialysis is used as an UF strategy and those with heart failure and end-stage renal disease in whom peritoneal dialysis is the renal replacement therapy of choice (CKD Stage V). Studies of peritoneal dialysis in heart failure patients with CKD and refractory fluid overload have shown this modality is associated with weight loss, improved quality of life, and reduction in heart failure hospitalizations and increase in LVEF.[167–170] However, these studies lack a control group, have a short follow-up, and insufficient power to detect an effect on mortality.

During the first 60–90 min of intraperitoneal dwell of dextrose-containing peritoneal dialysis solutions, rapid transport of free water across the aquaporin channels occurs, whereas the solute-rich water moves more slowly through the small pores of the peritoneal membrane. This results in an early drop in the concentration of sodium in the dialysate. This approaches the serum concentration as the diffusive movement of sodium continues and dwell time is sufficiently long.[166] The longer dwells of continuous ambulatory peritoneal dialysis may be preferred when sodium removal is the primary target, as it is in fluid-overloaded patients with heart failure.[170] Several strategies allow adequate sodium and water removal with automated peritoneal dialysis.[169] One approach is to substitute conventional dextrose-based dialysis solutions with icodextrin, a high molecular weight glucose polymer which induces transcapillary UF.[171] Another strategy is to decrease the number of nocturnal cycles to increase the dwell time. For patients with significant residual renal function, dietary sodium restriction and concomitant use of loop diuretics may enhance sodium removal by peritoneal dialysis.[172] Future studies should determine if peritoneal dialysis is associated with improved survival.

Short-term mechanical circulatory support

Among patients with advanced heart failure, short-term MCS may be indicated in the setting of

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cardiogenic shock. Several percutaneous and paracorporeal devices are available which can be used for a few days, up to several weeks, to allow cardiac recovery as well as recovery of other organs such as the kidneys, liver, and brain. Although insertion of most short-term devices is relatively simple and straightforward, the care of patients on short-term MCS requires specific expertise which should also include a plan when cardiac recovery does not occur after a period of support. In this way, short-term MCS can be used as a bridge-to-decision (BTD) for long-term MCS or heart transplantation.[173] As there is no single ideal device, their use should be primarily guided by clinical judgment and local experience.[174]

Intra-aortic balloon pump

An intra-aortic balloon pump (IABP) consists of a percutaneously implanted catheter with a balloon inflated with gas (usually helium, a low-density gas) that is positioned in the aorta between the left subclavian artery and the renal arteries. Intra-aortic balloon pumps have been used clinically for more than five decades. The mechanism of action is based on the principle of diastolic augmentation, i.e. the balloon is inflated during diastole and deflated during systole, thus facilitating coronary flow and improving oxygen supply to the myocardium and reducing afterload, thus reducing oxygen consumption. Its contribution to cardiac output is small, merely 0.5 L/min by some approximations. A small (n=10) study reported a median increase of 20% in cardiac index and significant reductions in left ventricular stroke work and left ventricular end-systolic pressure in patients undergoing IABP support before LVAD implantation.[175] Currently, IABP are primarily used for cardiogenic shock in the setting of acute ischaemic heart disease, and for protective support during high-risk percutaneous coronary intervention, but scientific evidence for these applications is lacking.[176,177] Intra-aortic balloon pumps are sometimes used to provide mechanical support to patients with cardiogenic shock prior to LVAD implantation, but the evidence for this practice is also limited. A small single-centre study (n=56) reported that IABP provided clinical stabilization in 57% of the patients who received IABP prior to LVAD implantation, whereas the remaining 43% had further clinical deterioration.[178] Higher right ventricular and left ventricular cardiac power indices and higher pulmonary artery pressure may predict patients more likely to respond to IABP.[178] In general, newer devices that generate greater support and provide better unloading of the left ventricle are currently preferred.

Extracorporeal membrane oxygenation

Extracorporeal membrane oxygenation (ECMO) is a cardiopulmonary bypass machine modified for easier and longer use and transport. Extracorporeal membrane oxygenation devices have a centrifugal blood pump that can provide up to 6 L/min of flow, as well as an oxygenator to provide full respiratory support. Thus, ECMO provides full systemic circulatory support and can be useful to restore end-organ perfusion.

Extracorporeal membrane oxygenation can be used in either veno–arterial or veno–venous configurations. The veno–arterial mode provides full cardiopulmonary support, while the veno–venous mode provides only respiratory support, i.e. oxygenation of venous blood, and it is used primarily in cases of severe respiratory insufficiency with preserved cardiac output. Extracorporeal membrane oxygenation can be configured with central or peripheral access. Central ECMO requires surgical access and cannulation of the ascending aorta, and it is predominantly used for postcardiotomy short-term MCS in patients who fail to wean off cardiopulmonary bypass. Conversely, peripheral ECMO can be placed by interventional cardiologists or trained intensivists using the Seldinger technique for insertion of cannulas in the femoral artery and vein.

Implantation and management of ECMO demands a dedicated team with expertise in this specific area. Perfusion technicians are essential for ECMO circuit priming and initiation; transoesophageal echocardiography or fluoroscopic guidance is advisable for cannula positioning, and vascular or cardiac surgeons must be available to manage possible vascular complications. Extracorporeal membrane oxygenation support demands anticoagulation with heparin; activated clotting time should be monitored frequently and maintained between 160–180 s. Complications of ECMO support are frequent and are mostly related to vascular complications, bleeding, thrombosis, and infections. In the case of peripheral ECMO, distal limb ischaemia remains relatively frequent despite the routine addition of a cannula for distal limb perfusion.

Although ECMO provides full support for the patient, it may have non-physiologic and sometimes detrimental haemodynamic consequences on the myocardium. Draining blood from the venous side results in a reduction of preload to the heart, and, consequently, reduces filling pressures of both ventricles. On the arterial side, ECMO delivers 4–6 L/min of flow to the aorta resulting in increased

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afterload to the left ventricle. Therefore, ECMO in itself does not necessarily decompress the heart, and depending on the severity of myocardial dysfunction and presence of aortic or mitral regurgitation, peripheral femoro–femoral ECMO may even increase left ventricular end-diastolic pressures and volumes. The resulting pulmonary venous congestion may lead to pulmonary oedema and compromise respiratory function.[179] In these cases, a few modifications in the ECMO circuit can be performed to optimize support, such as inserting a left atrial vent for unloading the pulmonary veins/left atrium (e.g. with central ECMO) or the left ventricular apex (e.g. with peripheral ECMO), or adding a second device to unload the left ventricle [e.g. IABP, Impella Ventricular Support Systems (Abiomed Inc., Danvers, MA, USA), or other short- to-medium-term surgically implanted MCS device].[180,181] Percutaneous left atrial septostomy has also been reported as a method to unload the left heart in ECMO-supported patients with refractory pulmonary oedema.[182] Native cardiac output and ECMO flow should be carefully balanced to prevent hypoxic blood perfusing the brain and the well-oxygenated blood mainly perfusing the rest of the body. Absence of native cardiac output may even result in complete clotting of the left ventricle despite adequate heparin treatment. ECMO can readily be used in cardiogenic shock caused by end-stage chronic heart failure as a short-term bridge-to-transplantation (BTT), BTD, or bridge-to-candidacy (BTC).[180,181] The SAVE score (www.save-score.com) can be used as a tool to predict survival in patients with cardiogenic shock in which ECMO is considered.[183] ECMO has been registered for use up to 30 days.

A recent meta-analysis of cohort studies suggested better survival rates and neurological outcomes in cardiac arrest patients when treated with ECMO in comparison to controls in whom ECMO was not used.[184] Furthermore, ECMO provided better survival in patients in cardiogenic shock when compared to IABP. The same effect was not observed when ECMO was compared to Impella or TandemHeart.[185]

TandemHeart® percutaneous ventricular assist device (Cardiac Assist, Inc., Pittsburgh, PA, USA)

TandemHeart is a device that connects the left atrium with the iliofemoral artery.[186,187] TandemHeart consists of a 21 Fr inflow cannula (inserted via the femoral vein to the right atrium and trans-septally into the left atrium), a centrifugal continuous extracorporeal blood pump, and an outflow arterial cannula (15-19 Fr, inserted in the iliofemoral artery). A membrane oxygenator can be added to the TandemHeart circuit to provide respiratory support. TandemHeart has Food and Drug Administration (FDA) approval for 6 h of support and also CE mark, which includes approval for Protec Duo veno–venous cannula up to 30 days (www.tandemlife.com).

The need for trans-septal puncture and positioning of the inflow cannula into the left atrium demands proficiency in its use. This makes the implant procedure more complex and longer as compared to other short-term percutaneously implanted devices.

The main advantages of this device are the direct unloading of the left atrium which results in a decrease in left ventricular filling pressures, volumes and oxygen demand and that it does not require passage into the left ventricle. However, positioning of the cannula in the left atrium carries a risk of complications, such as perforation, or most frequently, cannula migration to a suboptimal position or back to the right atrium. Furthermore, pumping blood out of the left atrium depends on preload to the left ventricle. TandemHeart can be easily configured to a right ventricular support system (TandemHeart RVAD).[188]

Other contraindications include significant peripheral vascular disease, general contraindications for anticoagulation therapy, presence of right or left atrial thrombi, ventricular septal defect, or severe aortic insufficiency. Anticoagulation therapy is mandatory due to the high risk of thromboembolic events. Requirements for activated clotting time are even higher than for ECMO, and should be around 300 s, which significantly increases the risk of bleeding complications.

Other important complications of TandemHeart support are vascular site complications, infections, and thromboembolic incidents. The major disadvantage is the immobility of the supported patient; care providers must secure the inflow cannula since movement of the tip from the left to right atrium results in significant right-to-left shunting with catastrophic desaturation.

TandemHeart improves haemodynamics by adding up to 4 L/min of cardiac output and lowering pulmonary capillary wedge pressure. However, a positive effect on survival has not been established in studies performed to date.[189,190]

Impella® ventricular support systems (Abiomed Inc., Danvers, MA, USA)

The Impella device is a small axial flow pump placed across the aortic valve, aspirating blood from the left ventricle and expelling it to the ascending aorta. In this way, it unloads the left ventricle, improving

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haemodynamics combined with decreasing pulmonary capillary wedge pressure, and increasing coronary artery flow. Contraindications include severe aortic valve disease (both stenosis and regurgitation), implanted mechanical aortic valve, or existence of left ventricular thrombus. Impella is manufactured in three versions: 2.5 device (12 Fr, maximum flow 2.5 L/min), CP device (14 Fr, maximum flow 2–4 L/min), and 5.0 device (21 Fr, maximum flow 5 L/min). Impella 5.0 is not fully percutaneous and requires a surgical procedure to insert a 21 Fr catheter in the femoral artery. Preliminary experience with the transaxillary approach has been reported.[191]

The distal tip of the catheter is designed as a pigtail catheter which contributes to stability in the left ventricular cavity and reduces suction events. Survival benefit with the 2.5 device in cardiogenic shock could not be demonstrated, and it is generally advised to use either the CP device or the 5.0 device in such cases.[192] Recent results suggest that when used as part of a standardized protocol in patients with cardiogenic shock and isolated left ventricular failure, early active haemodynamic support with Impella CP may be associated with improved outcomes and lower than previously reported or predicted mortality rates.[193]

The Impella device is FDA approved for partial support of up to 6 days, and it has a CE mark for up to 5 days. As with all peripheral percutaneous devices, peripheral artery disease is a contraindication to its use, as well as the inability to anticoagulate patients for any reason. Major complications of Impella use are associated with vascular injury, bleeding, thrombosis, haemolysis, and device migration. Recently, Impella has been shown also as an option for acute right ventricular support or for left ventricular unloading during ECMO.[181,194]

CentriMag acute circulatory support system (St. Jude, Minneapolis, MN, USA)

The CentriMag is a magnetically levitated paracorporeal centrifugal pump which can be used for left ventricular, right ventricular, and biventricular support. It requires surgical implantation by way of sternotomy but results in full circulatory support and complete cardiac unloading. Maximal flow is 10 L/min and duration of support is intended for up to 30 days, but longer is possible. It requires anticoagulation with intravenous heparin. This device can be used as a bridge-to-recovery or as a BTD for those patients who need a longer duration of support than is feasible by the previous mentioned devices. Also, the possibility of right ventricular support can be an advantage.[195,196] A new approach, minimally invasive CentriMag support integrated with ECMO (Ec-VAD) not requiring a sternotomy has been reported.[197] The Ec-VAD circuit is configured with left ventricular apical cannulation via mini-thoracotomy and femoral venous cannulation as inflows and right axillary artery cannulation as an outflow.

Long-term management of advanced heart failure

Advanced heart failure therapies are indicated when guideline-directed medical and device therapies have been implemented and optimized as appropriate in the individual patient but heart failure has progressed such that symptoms can no longer be adequately managed or end-organ function is compromised. Although details on guideline-directed medical and device therapies for chronic heart failure are not described herein, physicians should refer to existing guideline documents[9] to ensure optimization prior to considering advanced heart failure therapies, and for guidance on the continued management of these patients.

Conventional cardiac surgery

For patients with an LVEF ≤35% and coronary artery disease amenable to surgical revascularization, coronary artery bypass grafting in addition to medical therapy significantly reduced the primary outcome of all-cause death, and the secondary outcomes of cardiovascular death and all-cause death or cardiovascular hospitalization compared to medical therapy alone over 10 years of follow-up in the Surgical Treatment for Ischemic Heart Failure (STICH) trial.[198,199] Coronary artery bypass graft surgery is recommended for such patients with left main stenosis or left main equivalent.[200] For patients with unacceptably high surgical risk, coronary intervention is an option and may be facilitated under protection using an Impella device.[201]

In severe symptomatic aortic valve stenosis with mean gradient >40 mmHg, aortic valve replacement (AVR) is recommended irrespective of the degree of left ventricular dysfunction. In patients with prohibitive surgical risk due to co-morbidities but with projected survival >1 year after aortic valve

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intervention, transcatheter aortic valve implantation should be considered. In 'true' low-flow, low-gradient severe aortic stenosis[202] (valve area <1 cm^2, mean gradient <40 mmHg, stroke volume index <35 mL/m^2), with a depressed LVEF, left ventricular function usually improves after AVR if left ventricular dysfunction is due to excessive afterload; however, outcome is less certain if left ventricular dysfunction is due to scarring. In severe aortic regurgitation, AVR is recommended in all symptomatic patients as well as asymptomatic patients with LVEF ≤50%.[202] According to the most recent valvular guidelines, 'in patients with severe secondary mitral regurgitation and LVEF <30% who remain symptomatic despite optimal medical management (including CRT if indicated) and who have no option for revascularization, the Heart Team may consider a percutaneous edge-to-edge procedure or valve surgery after careful evaluation for a ventricular assist device or heart transplant according to individual patient characteristics.'[202] Additionally, 'in patients with LVEF <30% and severe functional mitral regurgitation due to coronary artery disease, but with evidence of myocardial viability, mitral valve surgery should be considered with revascularization.'[202] However, there is a legitimate concern that the more advanced the heart failure stage, the less likely that a mitral repair operation or clip procedure can benefit the patient. The ongoing COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation, NCT01626079) will evaluate the safety of the MitraClip system in 610 patients with heart failure and its effects on death and heart failure hospitalization.

Heart transplantation

Heart transplantation is the treatment of choice for carefully selected patients with advanced or end-stage heart failure. Although controlled trials have never been conducted, there is consensus within the cardiology community that heart transplantation significantly improves survival, exercise capacity, quality of life and return to work compared with conventional treatment, provided that proper selection criteria are applied (*Table 8*).[9,25] The main limitation of heart transplantation is the limited supply of donor hearts, which can vary substantially by country. Availability may impact indications and contraindications for heart transplant applied locally.

Since the first case of human heart transplant in 1967,[203] post-transplant survival has improved because of developments in recipient and donor selection, immunosuppression, and management of infectious complications. Thus, heart transplantation is now considered the gold standard therapy for refractory heart failure. Data from the latest International Society for Heart and Lung Transplantation (ISHLT) Registry shows 1-year survival of around 90% and median survival of 12.2 years.[19] Transplantation not only improves survival but also functional status and quality of life. At 1 to 3 years post-cardiac transplant, the proportion of survivors capable of normal activity (defined as physician-rated Karnofsky score 80–100%) is 90%.[204] The main challenges after heart transplantation are the consequences of both limited effectiveness and complications of immunosuppressive therapy (e.g. infections, antibody-mediated rejection, cardiac allograft vasculopathy, late graft dysfunction, malignancy, renal dysfunction, hypertension, diabetes mellitus).[204]

The patient evaluation before listing for transplant involves four main considerations. First, the presence of refractory heart failure should be confirmed to ensure that there are no other treatable aetiologies or alternative explanations for advanced symptoms. This step is important to guarantee the patient's candidacy for cardiac transplant and to reserve scarce donor organs for patients with the greatest need. Second, prognosis should be estimated. The greatest survival benefit is achieved in patients with a high mortality risk without heart transplant that also have a good expected survival post-transplant.[205] Third, co-morbidities should be evaluated to detect conditions that may negatively affect surgical and/or post-transplant outcomes or require special management.[25,204] Diagnostic and other tests [e.g. complete medical history, physical examination, CPET,[25,88] right heart catheterization, evaluation of peripheral vascular disease, assessment of frailty and nutritional status,[206] determination of organ function (lung, liver and kidney), screening for neoplasms or active infections],[25] prognostic scores (e.g. HFSS,[133] SHFM,[109] IMPACT[207]), and other studies as indicated based on co-morbidities (*Table 9*)[208–213] are used to assess these three components of the pre-cardiac transplant evaluation. Other health maintenance assessments should be performed (e.g. vaccination status) and addressed as clinically indicated. Blood group compatibility is mandatory for adult heart transplant patients. HLA antibody assessment is recommended; however, there is no consensus regarding the level and type of antibodies that contraindicate a specific donor.[214] Finally, a complete psychosocial evaluation should be included in the evaluation of all heart transplant candidates during the initial screening process to identify social and behavioural factors that may cause difficulties during the waiting period, convalescence, and long-term

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follow-up, particularly regarding substance abuse, adherence to therapy and follow-up visits.[213] Assessing that the patient has adequate social support (i.e. family or friends able to give support and who are willing to make long-term commitments for the patient's welfare) is also a critical component.[215] An important aspect of the pre-transplant cardiac evaluation is the identification of those patients who do not yet need a heart transplant and should either not be listed or removed if already listed with close monitoring and follow-up.

Some aetiologies of advanced heart failure (e.g. hypertrophic cardiomyopathy, restrictive cardiomyopathy, arrhythmogenic right ventricular dysplasia, complex congenital heart disease, and infiltrative cardiomyopathies) require specific approaches to diagnosis, prognosis, and determination of transplant eligibility, as described elsewhere.[25] Patients with restrictive cardiomyopathy and severe heart failure symptoms may be candidates for cardiac transplantation. Collaboration with other specialties is necessary to manage other organ systems impacted by these diseases. For example, in addition to heart transplantation, a hepatic transplant may be required for familial amyloidosis related to mutations in the transthyretin gene, or an autologous stem cell transplantation may be indicated for light chain amyloidosis.[25] Special considerations are needed for patients with congenital heart disease and in recipients that harbour chronic infections (e.g. Chagas disease, tuberculosis, human immunodeficiency virus, hepatitis C, and hepatitis B).[25]

Unstable patients

Pre-operative clinical stability is a strong predictor of early post-transplant outcomes; however, clinical instability can also be a priority criterion in some countries for organ allocation. Mechanical circulatory support systems can bridge selected patients to transplantation who are extremely ill and have a high-expected mortality while awaiting a suitable donor heart. Short-term MCS can also serve as a bridge in patients initially ineligible for transplantation, such as those in cardiogenic shock with end-organ damage. In these cases, short-term MCS may stabilize haemodynamics and end-organ perfusion and permit an evaluation of candidacy (e.g. determine extent of brain damage or other end-organ injury post-resuscitation).[9,173] Although urgent cardiac transplant listing is possible in many countries, the appropriateness of this strategy is now being debated. Among patients listed for emergent cardiac transplant in the Spanish National Heart Transplant Registry database, recipients meeting the INTERMACS profile 1 criteria (cardiogenic shock) and profile 2 criteria (progressive clinical decline despite treatment with inotropes) had the highest risk of primary graft failure, dialysis requirement, and in-hospital mortality following heart transplantation.[216] Therefore, in these critically ill patients, short-term MCS as a BTD might constitute a more reasonable initial strategy than an urgent transplant.

Long-term mechanical circulatory support

Long-term support with durable MCS devices like LVAD in patients with advanced heart failure has survival benefits and improves quality of life compared with conventional treatments in inotrope-dependent patients or in patients with contraindications for heart transplantation.[9] The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial first showed improved 1-year survival in inotrope-dependent, transplant-ineligible patients with advanced heart failure treated with an LVAD, but 2-year survival was not statistically different.[217] Since then, technology of LVAD and conservative management have improved.[217,218] Managing patients with long-term MCS requires a multidisciplinary Heart Team approach, and by gaining experience, centres may actually improve patient survival.[219]

Originally considered only as a lifesaving therapy for patients who were ineligible for heart transplantation, the proportion of long-term MCS devices implanted for destination therapy (DT) to heart transplants is increasing.[220] This growth is due to a growing shortage of donor hearts, increasing numbers of advanced heart failure patients, and continuous improvements in MCS technologies and survival rates.

Patient selection for long-term durable mechanical circulatory support

The INTERMACS profiles can help identify potential candidates for MCS[221] (*Table 2*). INTERMACS profile 1 indicates critical cardiogenic shock with very limited time for decision and intervention. Similarly, INTERMACS profile 2 indicates progressive decline despite inotropic support. In these patients, many centres prefer to use either paracorporeal or percutaneous short-term assist devices as a BTD. Long-term MCS devices are also an option for these patients. INTERMACS 3 patients are those who are stable on

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inotropes and are optimal candidates for implantable MCS, as their outcomes are significantly better than patients categorized as INTERMACS 1 or 2, and the potential for benefit overwhelms the risks of complications. Data from selected retrospective studies showed that survival rates were even better in non-inotrope dependent NYHA class IV patients or advanced NYHA class III patients (INTERMACS profiles 4–7).[151,222,223] A prospective, non-randomized, observational, propensity-adjusted study comparing LVAD with optimal medical management showed that a greater proportion of patients treated with LVAD survived for 12 months and had improvement in 6-min walk distance, along with a higher rate of adverse events and hospitalizations, compared to those receiving optimal medical management.[151]

Although INTERMACS profiles alone are insufficient to evaluate an individual patient for MCS, based on available data selected INTERMACS 1–2 patients and all INTERMACS 3 patients should be considered for MCS. Furthermore, carefully selected INTERMACS 4–7 patients who are willing to accept a risk of adverse events in exchange for potentially longer survival and better functional status can be considered for MCS.[104,151,224] In addition to INTERMACS profiles 1–2, risk factors for early mortality after MCS system implantation include renal dysfunction, elevated bilirubin, advanced age, female gender, presence of right heart failure and need for concomitant cardiac surgery.[225–227]

Patient selection for MCS overlaps with indications for heart transplantation.[25] However, as heart transplantation is still the gold standard, the use of LVAD therapy should be projected in light of the possibility to offer transplant opportunity to the patient, and it would be advisable that indications/contraindications to transplant are ruled out by the transplant centre *before* a device is implanted. Based on this concept, LVADs may be implanted according to three major treatment strategies: BTT, BTC and DT. In rare circumstances, LVAD therapy may lead to a recovery of heart function (bridge to recovery). In this context, however, in countries with low or declining transplant rates, implanting an LVAD as a BTT usually becomes DT, unless pump-related complications occur such as chronic driveline infection, bleeding, or thrombosis.

High pulmonary vascular resistance or transpulmonary gradient, or a recently treated cancer are contraindications for heart transplantation but not for MCS. On the other hand, severe right ventricular dysfunction[228] is a contraindication for LVAD, because there are still no good long-term solutions for right ventricular or biventricular mechanical support. Severe renal insufficiency is a contraindication for heart transplantation, but renal or liver function may improve after MCS,[229] as may pulmonary vascular resistance.[230] Thus, with the exception of advanced age or other irreversible contraindications for transplant, MCS should primarily be considered as BTC rather than DT. However, some patients with MCS will develop contraindications for transplantation over time.[231]

In general, early referral of patients with advanced heart failure to transplant and MCS centres can assure the best timing and outcomes for both transplantation or long-term MCS. Early referral applies to a wide spectrum of patients ranging from housebound NYHA class IV patients with poor exercise capacity despite optimal medical treatment plus CRT if needed, to NYHA class IV patients who are refractory to conventional treatments. Shared decision making is an important component of determining the appropriateness of long-term MCS.[232]

Adverse events and morbidities related to mechanical circulatory support

MCS-specific infections may be on the hardware itself or the body surfaces that contain them and include infections of the pump, cannula, anastomoses, pocket, or the percutaneous driveline or tunnel.[233] Driveline exit site infection is a common complication, occurring in 20–25% of patients (data from main randomized clinical trials),[234,235] but the majority remain superficial and can be managed by antibiotics.[236] Exit site swabs and blood cultures are obligatory when driveline infection is suspected. Resistant and complicated driveline infections (i.e. ascending driveline or pump pocket infection) can be an indication for listing the patient for urgent heart transplantation if there are no contraindications.[224] The ISHLT standardized definitions for MCS infections to differentiate ventricular assist device (VAD)-specific infections, VAD-related infections, and non-VAD infections.[233] Driveline infection can be further classified into superficial and deep according to surgical/histology, microbiology, and clinical criteria as well as general wound appearance.

Other complications include heart failure symptoms on MCS, which may be attributed to device failure, mechanical issues, or cannula malposition. Right ventricular dysfunction, new onset of right heart failure, aortic insufficiency, ascites, and cachexia are also important considerations.[224]

Treatment with anticoagulation and antiplatelet agents are mandatory to minimize the risk for pump thrombosis. Both embolic ischaemic events and bleeding events secondary to these therapies remain major complications of MCS and contribute to readmission and death.[237] Continuous flow devices have

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raised important considerations for haemocompatibility.[237] Routine monitoring of plasma-free haemoglobin and lactate dehydrogenase as haemolysis markers are useful for early detection of pump thrombosis. In HeartWare HVAD carriers, routine log-file review has demonstrated its usefulness for the early detection of pump thrombosis. In case of clinical suspicion, the diagnosis of pump thrombosis may be confirmed by means of an echocardiographic ramp test.[238]

Device selection

Currently, there are several vendors and a considerable number of devices that are used for medium-term and long-term MCS. Continuous flow implantable MCS devices of the second and third generation have shown significant superiority over pulsatile first-generation implantable MCS devices. Thus, in the last 15 years, the landscape of potential options in MCS has changed dramatically. Currently, the three MCS devices most often used are the HeartMate II, HeartWare HVAD, and HeartMate 3 (*Table 10*).[151,223,234,235,239–258] These devices have shown good durability, reasonable but still relatively high rates of device-related morbidity, improved functional capacity in implanted patients, and in the case of HeartMate 3, mid-term survival rates approaching that of post-transplant survival (overall 2-year survival of 83%). The incidence of adverse events with recent technological improvements (e.g. as with the fully magnetically-levitated HeartMate 3 potentially almost eliminating pump thrombosis) has reduced the rates of reoperation to replacement or removal a malfunctioning device, and disabling strokes, although the incidence of other adverse events is similar between newer and older devices.[258] Particular concern exists with stroke rates, especially with the HVAD device (29% at 2 years), and the HeartMate 3 has demonstrated a halving of stroke rates at 2 years compared to the HeartMate II device.[258] Minimally invasive VAD implantation methods will hopefully further benefit the overall outcome of patients, but structured investigation of these techniques is needed. Although minimally invasive techniques avoid the need for open sternotomy, they also have a greater potential for malposition, the same cumulative incisional length, and still require an open sternotomy if the right ventricle fails.[259] New technological breakthroughs are expected in the future (e.g. fully implantable pumps with transcutaneous energy transmission).[258] Importantly, appropriate long-term solutions for cases of severe right heart or biventricular failure remain an unmet need, as neither biventricular support with VADs or the total artificial heart can ensure a satisfactory quality of life and acceptable adverse event profile.

Palliative care of patients with advanced heart failure

Optimal care of patients with advanced heart failure includes palliative care at their end-of-life period and whenever appropriate during the patient journey. Conventional therapy (cardiologic therapeutic approach) may not sufficiently reduce patient suffering and maximize quality of life.

Successful palliative care must involve shared care through a multidisciplinary approach. Patients and their caregivers should be able to easily communicate with primary care, specialist palliative care services and the specialized advanced heart failure service, according to the resources of each centre.[9,131,260,261] Aging, co-morbid conditions, end-organ damage, cognitive impairment, frailty and limited social support complicate heart failure management, and palliative care should address each of these components. End-of-life decision making is even more challenging for patients with advanced heart failure when heart transplantation or long-term MCS have failed.[262] The PAL-HF (Palliative Care in Heart Failure) trial, a single-centre study of 150 patients, showed that interdisciplinary palliative care intervention in advanced heart failure patients resulted in greater benefits in quality of life, anxiety, depression and spiritual wellbeing compared with usual care alone.[263] The SWAP-HF (Social Worker-Aided Palliative Care Intervention in High-risk Patients with Heart Failure) trial showed that patients at high risk for mortality from heart failure frequently overestimate their life expectancy and a structured social worker-led palliative care intervention enhances prognostic understanding and patient–physician communication regarding goals of care.[264]

Communication with advanced heart failure patients is complex. In heart failure, the trajectory of each patient is different. Stocker *et al*.[265] showed that the majority of patients with heart failure reject the idea of heart failure as a terminal disease and prefer to focus on day-to-day management and maintenance, despite obvious deterioration in disease stage and needs over time. Common expectations pre- and post-heart transplant or MCS and potential complications should be discussed with patients and their caregivers, ideally, during the assessment and evaluation period for advanced heart failure therapies. Whenever possible, goals and preferences for end-of life issues should be discussed, especially in patients treated with MCS for DT. Living will and advance directive preferences are useful, and patients should be

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encouraged to prepare the necessary documents. A comprehensive end-of life plan of care for each patient should be available. This plan of care should be defined before MCS implantation or heart transplantation and revisited during the course of care.[262]

Patients with MCS as DT are particularly complex. A study at the Mayo Clinic on end-of-life care in long-term MCS patients showed that 78% of the patients who died were hospitalized, and of these, 88% died in the intensive care unit. The main causes of death were multiorgan failure, haemorrhagic stroke, and heart failure.[266] Goals of palliative care include management of physical symptoms (e.g. heart failure symptoms, pain, anxiety, depression, anorexia, constipation, and insomnia). Psychosocial and spiritual concerns should also be addressed.

An important aspect is deciding when to discontinue advanced therapies (e.g. MCS, ICD, or immunosuppressive treatment). This decision should be the patient's whenever possible, or the patient's caregiver, family, or hospital ethics committee if the patient is unable to independently convey their decisions. Support can be discontinued in the hospital, in hospice, or at home depending on patient and family preferences, feasibility, and local resources. Nurses and health care personnel involved should be adequately trained to correctly deactivate devices and associated alarms and to provide comfort care to the patient and psychological support to the family and care team.

Organizational issues for patient referral to advanced heart failure centres: hub and spoke network

The broad spectrum of heart failure ranges from patients in the early stages of the disease largely managed by primary care physicians and secondary care cardiologists, to those who progress to more advanced stages and require specialized tertiary care. All heart failure patients should undergo regular follow-up to detect progression of symptoms and disease. The criteria for referral to an advanced heart failure tertiary hub centre, i.e. those with capabilities for heart transplantation and MCS, must be based on need (i.e. indication) and eligibility (i.e. absence of contraindications) for those therapies, as well as the need for other advanced therapies for symptom management that may be unavailable at non-specialized centres (e.g. UF, peritoneal dialysis). A useful mnemonic has been proposed to aid in the identification of patients with advanced heart failure and timely referral for consideration of advanced therapies (*Table 11*).[267,268]

Ideally, secondary care centres without advanced heart failure therapies (spoke centre) should liaise with a tertiary hub centre to develop a strong working relationship. Heart failure patients are then managed within this 'hub and spoke' continuum of care (*Figure 2*). Spoke centres are responsible for ensuring adherence to guideline-directed therapy and that patients are referred to the tertiary hub centre at the appropriate time (*Figure 1*).

Each country should define the standards and organizational structures for advanced heart failure tertiary hub centres regarding pathways for referring patients, which should be made available to every patient, in relation to his/her individual characteristics and needs.[260,269–271] The tertiary hub centre should ensure that spoke centres know how to communicate in an agile way (telephones, email address) including urgently, if necessary. Once a patient is referred for evaluation, the hub and spoke centre teams should jointly agree whether the consultation can be done on an outpatient basis or requires an inpatient transfer between the two hospitals.

A protocol for the immediate management and safe transfer of unstable patients in cardiogenic shock must be developed and available at each tertiary hub centre, both for *de novo* patients and those with chronic, deteriorating heart failure. This protocol must be individualized, taking into account geographical considerations and resource availability at each spoke,[272–276] including in some cases a team dispatched from the tertiary hub centre to retrieve the patient.[277,278]

While the patient is on the waiting list for heart transplantation, decisions regarding cardiovascular care must be guided by the advanced heart failure team at the tertiary hub. However, the spoke centre physician has a key role in monitoring the patient's condition and implementing therapeutic decisions. Two-way communication between spoke and hub centres is key for the successful management of the patient.[260] Tertiary hub centres must provide education on advanced heart failure therapies and share their experience with spoke centres.

Principles of shared care after heart transplantation or mechanical circulatory support

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As the numbers of patients receiving heart transplants are plateauing or declining, there is an increasing need for more long-term MCS implantations. These advanced therapies should preferably be established within centres that offer both transplantation and MCS, although consensus has not been reached regarding this issue. Each hub and spoke centre should develop their own pathways for shared care.

Follow-up of patients after heart transplantation or implantation of MCS devices consists of both immediate post-operative period and long-term follow-up. In the immediate post-transplant or post-MCS implantation, care should be shared among intensivists, surgeons and cardiologists. In the early phase, haemodynamic monitoring is of great importance for both therapies, allowing for more accurate titration of inotropic or vasodilator therapy. Haemodynamic monitoring, along with echocardiographic imaging, allows for early detection of some of the potential adverse events that might occur in the immediate post-operative period (e.g. hypovolaemia, tamponade, acute right heart failure). Echocardiography is an integral part of cardiac allograft evaluation as well as device optimization, which includes setting the pump speed of the device and adjusting medical therapy to achieve optimal unloading of the left ventricle, while balancing the preload provided to the right ventricle.

Long-term follow-up of patients with advanced heart failure therapies is ideally done through the outpatient clinic. At each appointment for patients with long-term MCS, patient history and physical examination and laboratory assessment (e.g. haemolysis, anaemia, liver, renal, and infection markers) should be performed, with special attention to blood pressure, signs of congestion, shortness of breath, potential infection, bleeding, thrombosis, and the patient's general condition. For a patient with long-term MCS, the driveline exit site should be meticulously inspected for potential infection. The driveline, exit site, and other MCS system components should be examined to ensure their integrity. Blood pressure should be measured (preferably assisted with a Doppler ultrasonic device in patients with low pulsatility) and lowered if indicated. Blood pressure control is important since the risk of stroke is closely related to blood pressure for some devices like the HVAD. Mean arterial pressure should be maintained <90 mmHg, and ideally <85 mmHg. Regular echocardiographic assessment should be performed, determining the need for device optimization, e.g. increasing or decreasing the device speed, depending on the position of the interventricular septum, opening of the aortic valve, or size of the left ventricle. Alarm history should be obtained at regular intervals. If possible, functional testing should be performed (e.g. 6-min walking distance). Special attention should be directed at maintaining adequate anticoagulation status, and if available self-monitoring should be encouraged. Patients should be regularly educated on proper care of the driveline exit site.

Post-transplant patients should undergo a pre-defined regimen of graft biopsies, titration of immunosuppressive and other therapies, rejection monitoring, assessment for infections, transplant coronary artery disease and/or cardiac allograft vasculopathy, immunosuppression side effects, and other potential complications including neoplasia, and co-morbidities that require comprehensive treatment. Shared care with referral cardiologists and primary care physicians is needed.

Treatment and follow-up of patients who are post-cardiac transplant or MCS recipients requires an interdisciplinary approach to meet the complex needs of these patients. In addition to the transplant cardiologist and MCS device specialist, a dedicated transplant/MCS device nurse is important to educate the patient and caregivers, as well as coordinate health care team members. A cardiac surgeon should also be included in case of surgical complications. For patients with MCS, driveline infection is primarily a surgical problem. Ideally, a nutritionist, physiotherapist, psychologist, psychiatrist, and general practitioner should also be a part of the team taking care of patients treated with advanced heart failure therapies. Depending on co-morbidities and complications, other specialists should participate in shared care as appropriate. Highly experienced tertiary centres are required to provide this multidisciplinary approach to shared care and address the needs of heart failure patients managed with advanced therapies.

Conclusion

Advanced heart failure remains a major clinical challenge. Changes in the clinical characteristics and clinical practice of heart failure treatment have made it necessary to develop the present update of the original criteria for the definition of advanced heart failure. New biomarkers and imaging tools may allow better prognostic stratification and the assessment of mechanisms of disease progression. However, robust data are lacking from prospective, controlled trials demonstrating the clinical usefulness of these new methods. Once guideline-directed management therapy is insufficient, the patient may benefit from advanced heart failure therapies. Inotropic agents have frequently been used as intermittent intravenous

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infusions, but no definitive outcome data from prospective, randomized trials are available and some studies have shown an association with increased mortality. Thus, these agents provide only symptomatic treatment or stabilization in unstable conditions. Impressive progress has been made with MCS devices. At least four devices are available for the immediate treatment of cardiogenic shock. Heart transplantation is considered the treatment of choice for eligible patients with excellent survival and quality of life, but it is limited by organ availability, graft dysfunction, and side effects of immunosuppression. Long-term MCS can be used as a BTT or as DT. Recent improvement in the characteristics of MCS devices will broaden their indications and make them a valid alternative to medical treatment in patients with advanced heart failure. Lastly, palliative care is indicated when patients are ineligible for advanced heart failure therapies or after advanced therapies have been performed and patient progresses to end-of-life. Finally, it is important to note that no therapy in advanced heart failure is based on reliable prospective studies, and there is an urgent need to develop evidence-based treatment algorithms to prolong life, increase life quality, and reduce the burden of hospitalization in this vulnerable patient population.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:
Table S1. Ultrafiltration clinical trials: overview of study designs and key findings.

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Figure 1 Triage of patients with advanced heart failure (HF) and appropriate timing of referral. ARNI, angiotensin receptor–neprilysin inhibitor; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RAS, renin–angiotensin system; SBP, systolic blood pressure; SCr, serum creatinine.

Figure 2 Conceptual structure of a hub and spoke model of care for patients with advanced heart failure (HF). This figure presents a concept for the structure of a hub and spoke model of care for patients with advanced HF. The roles for primary care, general cardiology (yellow), specialized HF (orange), and tertiary centres (red) are described. Solid lines reflect main lines of communication and referral. Dashed lines indicate secondary pathways for referral/communication (i.e. typically patients will first be referred to a specialized HF unit, but in some circumstances direct referral to the tertiary hub bypassing the specialized HF centre may be appropriate.) This model depicts an overview of the concept, which can be tailored to the local needs of the health care system. CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator.

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Table 1 Prior definitions and indicators of advanced heart failure

Heart Failure Association[4]	American College of Cardiology / American Heart Association[5,6]	Heart Failure Society of America[3]
1. Severe symptoms of HF with dyspnoea and/or fatigue at rest or with minimal exertion (NYHA functional class III or IV) 2. Episodes of fluid retention (pulmonary and/or systemic congestion, peripheral oedema) and/or of reduced cardiac output at rest (peripheral hypoperfusion) 3. Objective evidence of severe cardiac dysfunction, shown by at least one of the following: a) A low LVEF (<30%) b) A severe abnormality of cardiac function on Doppler echocardiography with a pseudonormal or restrictive mitral inflow pattern c) High LV filing pressures (mean PCWP >16 mmHg, and/or mean RAP >12 mmHg by pulmonary artery catheterization) d) High BNP or NT-proBNP plasma levels, in the absence of non-cardiac causes 4. Severe impairment of functional capacity shown by one of the following: a) Inability to exercise b) 6MWT distance <300 m or less in females and/or patients aged ≥75 years c) Peak VO_2 <12 to 14 mL/kg/min 5. History of ≥1 HF hospitalization in the past 6 months 6. Presence of all the previous features despite 'attempts to optimize' therapy including diuretics, inhibitors of the renin–angiotensin–aldosterone system, and beta-blockers, unless these are poorly tolerated or contraindicated, and CRT, when indicated	1. Repeated (≥2) hospitalizations or ED visits for HF in the past year 2. Progressive deterioration in renal function (e.g. rise in BUN and creatinine) 3. Weight loss without other cause (e.g. cardiac cachexia) 4. Intolerance to ACE inhibitors due to hypotension and/or worsening renal function 5. Intolerance to beta-blockers due to worsening HF or hypotension 6. Frequent systolic blood pressure <90 mmHg 7. Persistent dyspnoea with dressing or bathing requiring rest 8. Inability to walk 1 block on the level ground due to dyspnoea or fatigue 9. Recent need to escalate diuretics to maintain volume status, often reaching daily furosemide equivalent dose >160 mg/day and/or use of supplemental metolazone therapy 10. Progressive decline in serum sodium, usually to <133 mEq/L 11. Frequent ICD shocks	The presence of progressive and/or persistent severe signs and symptoms of HF despite optimized medical, surgical, and device therapy. It is generally accompanied by frequent hospitalization, severely limited exertional tolerance, and poor quality of life and is associated with high morbidity and mortality. Importantly, the progressive decline should be primarily driven by the HF syndrome. Indicators of advanced HF in the setting of optimal medical and electrical therapies that should trigger consideration of referral for evaluation of advanced therapies include: • Need for intravenous inotropic therapy for symptomatic relief or to maintain end-organ function • Peak VO_2 <14 mL/kg/min or <50% of predicted • 6MWT distance <300 m • ≥2 HF admissions in the last 12 months • >2 unscheduled visits (e.g. ED or clinic) in the last 12 months • Worsening right HF and secondary pulmonary hypertension • Diuretic refractoriness associated with worsening renal function • Circulatory–renal limitation to RAAS inhibition or beta-blocker therapy • Progressive/persistent NYHA functional class III–IV symptoms • Increased 1-year mortality (e.g. 20–25%) predicted by HF survival models (e.g. SHFS, HFSS, etc.) • Progressive renal or hepatic end-organ dysfunction • Persistent hyponatraemia (serum sodium <134 mEq/L) • Recurrent refractory ventricular tachyarrhythmias; frequent ICD shocks • Cardiac cachexia • Inability to perform ADL

6MWT, 6-minute walk test; ACE, angiotensin-converting enzyme; ADL, activities of daily living; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CRT, cardiac resynchronization therapy; ED, emergency department; HF, heart failure; HFSS, Heart Failure Survival Score; ICD, implantable cardioverter-defibrillator; LV, left ventricular; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; RAAS, renin–angiotensin–aldosterone system; RAP, right atrial pressure; SHFS, Seattle Heart Failure Score; VO_2, oxygen consumption.

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Table 2 Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile descriptions in patients with advanced heart failure

Profile	Time frame for intervention
Profile 1: Critical cardiogenic shock Patients with life-threatening hypotension despite rapidly escalating inotropic support, critical organ hypoperfusion, often confirmed by worsening acidosis and/or lactate levels. "Crash and burn."	Definitive intervention needed within hours.
Profile 2: Progressive decline Patient with declining function despite intravenous inotropic support, may be manifest by worsening renal function, nutritional depletion, inability to restore volume balance. "Sliding on inotropes." Also describes declining status in patients unable to tolerate inotropic therapy.	Definitive intervention needed within few days.
Profile 3: Stable but inotrope-dependent Patient with stable blood pressure, organ function, nutrition, and symptoms on continuous intravenous inotropic support (or a temporary circulatory support device or both), but demonstrating repeated failure to wean from support due to recurrent symptomatic hypotension or renal dysfunction. "Dependent stability."	Definitive intervention elective over a period of weeks to few months.
Profile 4: Resting symptoms Patient can be stabilized close to normal volume status but experiences daily symptoms of congestion at rest or during ADL. Doses of diuretics generally fluctuate at very high levels. More intensive management and surveillance strategies should be considered, which may in some cases reveal poor compliance that would compromise outcomes with any therapy. Some patients may shuttle between 4 and 5.	Definitive intervention elective over a period of weeks to few months.
Profile 5: Exertion intolerant Comfortable at rest and with ADL but unable to engage in any other activity, living predominantly within the house. Patients are comfortable at rest without congestive symptoms, but may have underlying refractory elevated volume status, often with renal dysfunction. If underlying nutritional status and organ function are marginal, patients may be more at risk than INTERMACS 4, and require definitive intervention.	Variable urgency, depends upon maintenance of nutrition, organ function, and activity.
Profile 6: Exertion limited Patient without evidence of fluid overload is comfortable at rest, and with ADL and minor activities outside the home but fatigues after the first few minutes of any meaningful activity. Attribution to cardiac limitation requires careful measurement of peak oxygen consumption, in some cases with haemodynamic monitoring to confirm severity of cardiac impairment. "Walking wounded."	Variable, depends upon maintenance of nutrition, organ function, and activity level.
Profile 7: Advanced NYHA class III A placeholder for more precise specification in future, this level includes patients who are without current or recent episodes of unstable fluid balance, living comfortably with meaningful activity limited to mild physical exertion.	Transplantation or circulatory support may not currently be indicated.
Modifiers for profiles	**Possible profiles to modify**
TCS-Temporary Circulatory Support can modify only patients in hospital (other devices would be INTERMACS devices). This includes IABP, ECMO, TandemHeart, Levitronix, BVS 5000 or AB5000, Impella.	1, 2, 3 in hospital.
A-Arrhythmia can modify any profile. Recurrent ventricular tachyarrhythmias that have recently contributed substantially to clinical compromise. This includes frequent ICD shocks or requirement for external defibrillator, usually more than twice weekly.	Any profile.
FF-Frequent Flyer can modify only outpatients, designating a patient requiring frequent emergency visits or hospitalizations for diuretics, ultrafiltration, or temporary intravenous vasoactive therapy.	3 if at home, 4, 5, 6. A Frequent Flyer would rarely be profile 7.

ADL, activities of daily living; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; ICD, implantable cardioverter-defibrillator; NYHA, New York Heart Association.
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Table 3 Updated HFA-ESC criteria for defining advanced heart failure

All the following criteria must be present despite optimal guideline-directed treatment:

1. Severe and persistent symptoms of heart failure [NYHA class III (advanced) or IV].
2. Severe cardiac dysfunction defined by a reduced LVEF ≤30%, isolated RV failure (e.g. ARVC) or non-operable severe valve abnormalities or congenital abnormalities or persistently high (or increasing) BNP or NT-proBNP values and data of severe diastolic dysfunction or LV structural abnormalities according to the ESC definition of HFpEF and HFmrEF.[9]
3. Episodes of pulmonary or systemic congestion requiring high-dose intravenous diuretics (or diuretic combinations) or episodes of low output requiring inotropes or vasoactive drugs or malignant arrhythmias causing >1 unplanned visit or hospitalization in the last 12 months.
4. Severe impairment of exercise capacity with inability to exercise or low 6MWTD (<300 m) or pVO_2 (<12–14 mL/kg/min), estimated to be of cardiac origin.

In addition to the above, extra-cardiac organ dysfunction due to heart failure (e.g. cardiac cachexia, liver, or kidney dysfunction) or type 2 pulmonary hypertension may be present, but are not required.

Criteria 1 and 4 can be met in patients who have cardiac dysfunction (as described in criterion #2), but who also have substantial limitation due to other conditions (e.g. severe pulmonary disease, non-cardiac cirrhosis, or most commonly by renal disease with mixed aetiology). These patients still have limited quality of life and survival due to advanced disease and warrant the same intensity of evaluation as someone in whom the only disease is cardiac, but the therapeutic options for these patients are usually more limited.

ARVC, arrhythmogenic right ventricular cardiomyopathy; BNP, B-type natriuretic peptide; ESC, European Society of Cardiology; HFA, Heart Failure Association; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; LV, left ventricular; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; pVO_2, peak exercise oxygen consumption; RV, right ventricular; 6MWTD, 6-minute walk test distance.

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Table 4 Risk markers in patients with advanced heart failure

General clinical
Age[30]
Male sex[31]
↑ QRS duration[32,33]
Longer HF duration[30]
Higher NYHA class[34–37]
Lower and labile SBP and lower DBP and MAP[30,38–40]
Lower pulse pressure[41]
↑ HR in sinus rhythm but not in atrial fibrillation[30,42–44]
Reduced HR variability[45–47]
Recent /recurrent HF hospitalizations[30]
Haemodynamic profiles[48,49]
Cardiomegaly[30]
S3[50]
Poor quality of life
Reduced peripheral muscle strength[120]
Rales[30]
Oedema[30]
JVD[50]
Hepatomegaly
Ascites

Laboratory and biomarkers[121]
Copeptin[51, 122, 123]
Low sodium[52]
Cardiomyocyte injury
- Troponin[53-57]

Cardiomyocyte stress
- Higher BNP and/or NT-proBNP[56,58–62]
- Increased NT-proBNP over time[53,63]
- ANP[64]
- MR-proANP[62,124]

Inflammation
- CRP[65,66]
- ESR[67]

Oxidative stress and fibrosis
- ST2[56]
- Galectin-3[125]
- GDF-15[126]
- MR-proADM[68]
- Lower LDL
- Uric acid[69]
- Low T3[70]
- Albuminuria[71]

Imaging
Echocardiography
- Lower LVEF[72–74]
- Large areas of hypo/akinesis
- LV dilatation[74]
- Diastolic dysfunction[75,76]
- Mitral regurgitation[30]
- Aortic stenosis
- LV hypertrophy[72,77]
- LV mass[72]
- Left atrial enlargement[72,78,79]
- Right ventricular function[80,81]
- Pulmonary hypertension[80,82]
- Resting dobutamine stress strain[83,84]

Other imaging
- Pulmonary congestion by lung ultrasound[85]
- Inflammation and fibrosis on CMR
- Poor viability on stress echo and CMR[84]
- Reduced miBG uptake[86,87]

Cardiopulmonary exercise test
pVO_2[59,88]
6-min walk test[127]
V_E/V_{CO2} slope[25,64]

Co-morbidity
Cardiovascular
- Ischaemic heart disease/prior myocardial infarction[30]
- Prior transient ischaemic attack/stroke
- Peripheral arterial disease

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- Atrial fibrillation[30]
- Ventricular arrhythmia, sudden cardiac death, ICD shocks

Non-cardiovascular

- Chronic kidney disease[89,90]
- Diabetes[30]
- Chronic obstructive pulmonary disease
- Smoking[30]
- Anaemia[91]
- Higher red cell distribution width[92]
- Higher white blood cell count[93]
- Iron deficiency
- Liver dysfunction and low albumin[94,95]
- Sleep apnoea and Cheyne–Stokes breathing
- Depression[96–98]
- Frailty[99]
- Cachexia[30,100,101]
- Cognitive dysfunction[102]
- Diuretic resistance

Composite scores[27,28]

Simplified variables[103]

INTERMACS[8,104]

MAGGIC[105,106]

BIOSTAT-CHF[107]

BCN Bio-HF[108]

SHFM[109,110]

HFSS[111–117]

UCLA score[118]

Treatment and organization-related factors

Poor guideline adherence[119]

ANP, atrial natriuretic peptide; BCN Bio-HF, Barcelona Bio-Heart Failure; BIOSTAT-CHF, A Systems Biology Study to Tailored Treatment in Chronic Heart Failure; BNP, B-type natriuretic peptide; CMR, cardiac magnetic resonance; CRP, C-reactive protein; DBP, diastolic blood pressure; ESR, erythrocyte sedimentation rate; GDF-15, growth differentiation factor 15; HF, heart failure; HFSS, Heart Failure Survival Score; HR, heart rate; ICD, implantable cardioverter-defibrillator; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; JVD, jugular venous distention; LDL, low-density lipoprotein; LV, left ventricular; LVEF, left ventricular ejection fraction; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure; miBG, metaiodobenzylguanidine; MAP, mean arterial pressure; MR-proADM, mid-regional pro-adrenomedullin; MR-proANP, mid-regional pro-atrial natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; pVO_2, peak exercise oxygen consumption; SHFM, Seattle Heart Failure Model; SBP, systolic blood pressure; UCLA, University of California, Los Angeles; V_E/V_{CO2}, minute ventilation–carbon dioxide production relationship.

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Table 5 Prognostic scores

Score	Components	Comments
HFSS[133]	• Presence/absence coronary artery disease • Resting heart rate • Left ventricular ejection fraction • Mean arterial blood pressure • Presence/absence of intraventricular conduction delay • Serum sodium • Peak oxygen uptake HFSS = [(0.0216 * resting HR) + (−0.0255 * mean BP) + (−0.0464 * LVEF) + (−0.047 * serum sodium) + (−0.0546 * peak VO_2) + (0.608 * presence or absence of IVCD) + (0.6931 * presence or absence of ischaemic heart disease)]	Score is based on a sum of these variables multiplied by defined coefficients Low risk: ≥8.1 Medium-risk: HFSS 7.20 to 8.09 High-risk: HFSS ≤7.1
SHFM[109]	• Demographics • Clinical characteristics • Medications • Laboratory data • Devices www.seattleheartfailuremodel.org	Incorporates impact of interventions (medical and device) and provides estimates of 1, 2, and 5-year survival
MECKI[134–136]	• Percent predicted peak VO_2 • V_E/V_{CO2} slope • Haemoglobin • Serum sodium • LVEF • eGFR by MDRD	Incorporates data from the CPET as well as kidney function
MAGGIC[105]	• Age • Gender • LVEF • Systolic blood pressure • Body mass index • Serum creatinine • NYHA class • Smoking history • Co-morbidities (e.g. diabetes, COPD) • Length of heart failure diagnosis • Medications www.heartfailurerisk.org	Risk model converted into integer score Generalizable to a broad spectrum of patients

BP, blood pressure; COPD, chronic obstructive pulmonary disease; CPET, cardiopulmonary exercise test; eGFR, estimated glomerular filtration rate; HFSS, Heart Failure Survival Score; HR, heart rate; IVCD, intraventricular conduction defect; LVEF, left ventricular ejection fraction; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure; MDRD, Modification of Diet in Renal Disease; MECKI, Metabolic Exercise test data combined with Cardiac and Kidney Indexes; NYHA, New York Heart Association; SHFM, Seattle Heart Failure Model; V_E/V_{CO2}, minute ventilation–carbon dioxide production relationship; VO_2, oxygen consumption.

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Table 6 Suggested clinical, laboratory, and echocardiographic criteria to trigger referral*

Clinical	Laboratory	Imaging	Risk score data
• >1 HF hospitalization in last year • NYHA class III–IV • Intolerant of optimal dose of any GDMT HF drug • Increasing diuretic requirement • SBP ≤90 mmHg • Inability to perform CPET • 6MWT • CRT non-responder clinically • Cachexia, unintentional weight loss • KCCQ • MLHFQ	• eGFR <45 mL/min • SCr ≥160 mmol/L • K >5.2 or <3.5 mmol/L • Hyponatraemia • Hb ≤120 g/L • NT-proBNP ≥1000 pg/mL • Abnormal liver function test • Low albumin	• LVEF ≤30% • Large area of akinesis/dyskinesis or aneurysm • Moderate[†]-severe mitral regurgitation • RV dysfunction • PA pressure ≥50 mmHg • Moderate-severe tricuspid regurgitation • Difficult to grade aortic stenosis • IVC dilated or without respiratory variation	• MAGGIC predicted survival ≤80% at 1 year • SHFM predicted survival ≤80% at 1 year

6MWT, 6-min walk test; CPET, cardiopulmonary exercise test; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; GDMT, guideline-directed medical therapy; Hb, haemoglobin; HF, heart failure; IVC, inferior vena cava; K, potassium; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure; MLHFQ, Minnesota Living with Heart Failure Questionnaire; Na, sodium; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PA, pulmonary artery; RV, right ventricular; SBP, blood pressure; SCr, serum creatinine; SHFM, Seattle Heart Failure Model.

*Note that this table reflects many clinically relevant but sometimes subjective and non-specific criteria. With these criteria, sensitivity has been prioritized over specificity, i.e. many criteria may be present in patients who do not need referral, but by considering these criteria in a comprehensive assessment, there is a lower risk that high-risk patients may be missed or referred too late. While cut-offs exist for transplantation listing or left ventricular assist device implantation, there are no data to support specific cut-offs for referral to a HF centre.

†Moderate mitral regurgitation alone is not sufficient, but is one factor suggesting risk of progression and should be considered together with other variables.

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Table 7 Inotropes and vasoconstrictors

	Mechanism of action	Haemodynamic effect	Comment
Inodilators			
Dobutamine	Beta-1 activation, slight beta-2 vasodilatation	CO ↑, SVR ↓	Half-life minutes
Milrinone	PDE2 inhibition	CO ↑, SVR ↓	Half-life 2 h
Levosimendan	Calcium sensitization	CO ↑, SVR ↓	Half-life (metabolite) days
Inotropes/vasoconstrictors			
Dopamine	Beta-1, alpha-adrenergic, and dopaminergic activation	CO ↑, SVR ↑	2–10 μg/kg/min: beta-1 >10 μg/kg/min: alpha, beta-1
Adrenaline	Beta-1, alpha-adrenergic, moderate beta-2 activation	CO ↑, SVR ↑	
Vasoconstrictors			
Norepinephrine	Beta-1, alpha activation	SVR ↑, CO ↔/↓	
Vasopressin	V1 and V2 activation	SVR ↑, CO ↔/↓	

CO, cardiac output; PDE2, phosphodiesterase-2; SVR, systemic vascular resistance.

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Table 8 Indications and contraindications to heart transplantation

Patients to consider	1. End-stage HF with severe symptoms, a poor prognosis, and no remaining alternative treatment options 2. Motivated, well informed, and emotionally stable 3. Capable of complying with the intensive treatment required postoperatively
Contraindications	1. Active infection 2. Severe peripheral arterial or cerebrovascular disease 3. Pharmacologic irreversible pulmonary hypertension (LVAD should be considered with subsequent re-evaluation to establish candidacy) 4. Cancer (a collaboration with oncology specialists should occur to stratify each patient as to their risk of tumour recurrence) 5. Irreversible renal dysfunction (e.g. creatinine clearance <30 mL/min) 6. Systemic disease with multiorgan involvement 7. Other serious co-morbidity with poor prognosis 8. Pre-transplant BMI >35 kg/m^2 (weight loss is recommended to achieve a BMI <35 kg/m^2) 9. Current alcohol or drug abuse 10. Any patient for whom social supports are deemed insufficient to achieve compliant care in the outpatient setting

BMI, body mass index; HF, heart failure; LVAD, left ventricular assist device.
Adapted from Ponikowski *et al*.[9] and Mehra *et al*.[25]

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Table 9 Considerations in assessment of co-morbidities

Co-morbidity	Parameters to evaluate
Age[208]	Frailty
	Co-morbidity burden
	Local organ availability and quality
Obesity	Body mass index
Diabetes mellitus	End-organ damage (e.g. neuropathy, nephropathy)
	Glycated haemoglobin
Renal impairment	Estimated GFR
	Renal ultrasonography
	Proteinuria estimation
	Presence of renal arterial disease
	Candidacy for combined heart/kidney transplant[209]
Cancer	Active malignancy
	Collaboration with oncologist for prior cancer previously treated
	Previous tumour type, response to therapy
	Metastatic work-up
Cerebral or peripheral vascular disease	Diagnostic work-up as indicated to assess clinical severity
	Potential to limit rehabilitation
Substance abuse	Tobacco (including environmental or second-hand exposure)
	Alcohol
	Recreational drugs
HIV[210,211]	Active or prior opportunistic infections
	Adherence to combination anti-retroviral therapy
	HIV RNA
	CD4 count
Chagas disease[212]	Serology testing for *T. cruzi* in patients at risk
Hepatitis B and C	Antibody/antigen testing
	HCV RNA PCR
	Liver function tests
	Viraemia
	Serology
	Liver biopsy
Psychosocial	Complete evaluation
	Potential for adherence to therapy[213]

CD4, cluster of differentiation 4; GFR, glomerular filtration rate; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PCR, polymerase chain reaction; RNA ribonucleic acid.

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Table 10 Overview of long-term mechanical circulatory support devices

Device	Device characteristics	Evidence from major clinical trials	Major risks	Ongoing / future studies
HeartMate II (Thoratec, St. Jude, Abbott)[151,223,239–247]	Axial flow pump Implanted in pre-peritoneal pocket, connected via inflow cannula to left ventricular apex, and via outflow cannula to ascending aorta	BTT strategy (prospective, single-arm, *n*=133): 75% survival 6 months, 68% survival 12 months[239] HeartMate II LVAD[242] (randomized continuous flow vs. pulsatile): improved 2-year survival free of stroke or device failure for continuous flow vs. pulsatile ROADMAP[151,243] (observational, *n*=97 LVAD, *n*=103 OMM): LVAD associated with better survival and functional capacity at 2 years	Device failure Pump thrombosis[244–246] Ischaemic stroke Driveline infection[247] Bleeding (haemorrhagic stroke) RV failure	
HeartWare (HeartWare, Medtronic)[235,248–253,257]	Continuous flow centrifugal pump Implanted and positioned completely within pericardial space, connected via driveline to controller	Single-arm (transplant candidates, NYHA class IV, *n*=50): 84% 1-year survival[248] Post-CE mark approval registry (*n*=254): 85% 1-year survival, 73% 3-year survival[249] ADVANCE (HeartWare vs. commercially available LVADs): non-inferior to commercially available devices[257]; continued access protocol 84% 1-year survival[250] ENDURANCE (randomized, open-label, *n*=446 advanced HF ineligible for transplant, HeartWare vs. HeartMate II): non-inferiority of HeartWare vs. other devices for survival at 2 years free from disabling stroke or device removal; higher rate of stroke, RV failure, sepsis[235]	Ischaemic stroke Haemorrhagic stroke RV failure Infection Device failure[252,253] Pump thrombosis Driveline infection	
HeartMate 3 (St. Jude, Abbott)[234,254–256,258]	Continuous flow, centrifugal pump, bearing-less magnetically levitated rotor, artificial pulse	Single arm (*n*=50, BTT and DT): 98% 30-day survival, 92% 6-month survival; 1-year survival similar to other devices[254,255] MOMENTUM 3 (randomized, HeartMate 3 vs. HeartMate II, both BTT and DT, *n*=294): centrifugal flow pump non-inferior to axial-flow pump at 6 months; superiority also established (HR 0.55, 95% CI 0.32–0.95, *P*=0.04)[234] MOMENTUM 3 2-year outcomes (*n*=366): – Survival free of disabling stroke or survival free of reoperation to replace/remove device: HR 0.46, 95% CI 0.31–0.69, *P*<0.001 (superiority)[258] – Rate of stroke: 10.1% vs. 19.2% (HR 0.47, 95% CI 0.27–0.84, *P*=0.02)	No pump thrombosis in MOMENTUM 3 compared to 10.1% in axial flow group RV failure Stroke Infection Driveline infection	MOMENTUM 3: randomized, HeartMate 3 vs. HeartMate II, both BTT and DT (long-term outcomes)[256]

ADVANCE, Evaluation of the HeartWare Left Ventricular Assist Device for the Treatment of Advanced Heart Failure; BTT, bridge to transplant; CI, confidence interval; DT, destination therapy; ENDURANCE, Evaluation of the HeartWare Ventricular Assist System for Destination Therapy of Advanced Heart Failure; HF, heart failure; HR, hazard ratio; LVAD, left ventricular assist device; MOMENTUM, Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3; NYHA, New York Heart Association; OMM, optimal medical management; ROADMAP, Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients; RV, right ventricular.

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Table 11 'I Need Help'—Markers of advanced heart failure

I	**I**notropes	Previous or ongoing requirement for dobutamine, milrinone, dopamine, or levosimendan
N	**N**YHA class/natriuretic peptide	Persisting NYHA class III or IV and/or persistently high BNP or NT-proBNP
E	**E**nd-organ dysfunction	Worsening renal or liver dysfunction in the setting of heart failure
E	**E**jection fraction	Very low ejection fraction <20%
D	**D**efibrillator shocks	Recurrent appropriate defibrillator shocks
H	**H**ospitalizations	More than 1 hospitalization with heart failure in the last 12 months
E	**E**dema/escalating diuretics	Persisting fluid overload and/or increasing diuretic requirement
L	**L**ow blood pressure	Consistently low BP with systolic <90 to 100 mmHg
P	**P**rognostic medication	Inability to up-titrate (or need to decrease/cease) ACEI, beta-blockers, ARNIs, or MRAs

ACEI, angiotensin-converting enzyme inhibitor; ARNI, angiotensin receptor–neprilysin inhibitor; BNP, B-type natriuretic peptide; BP, blood pressure; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.
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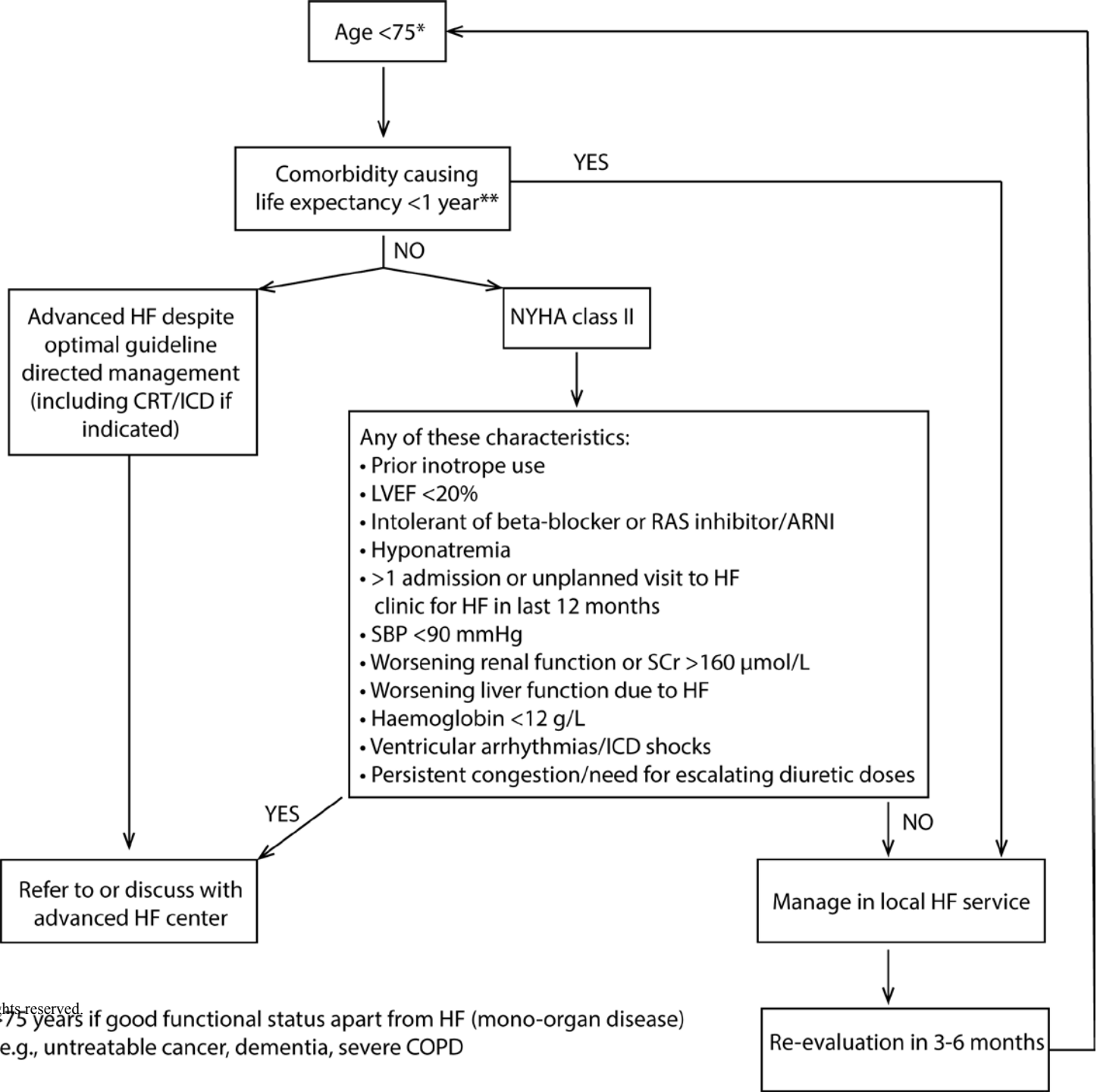
Figure 1.



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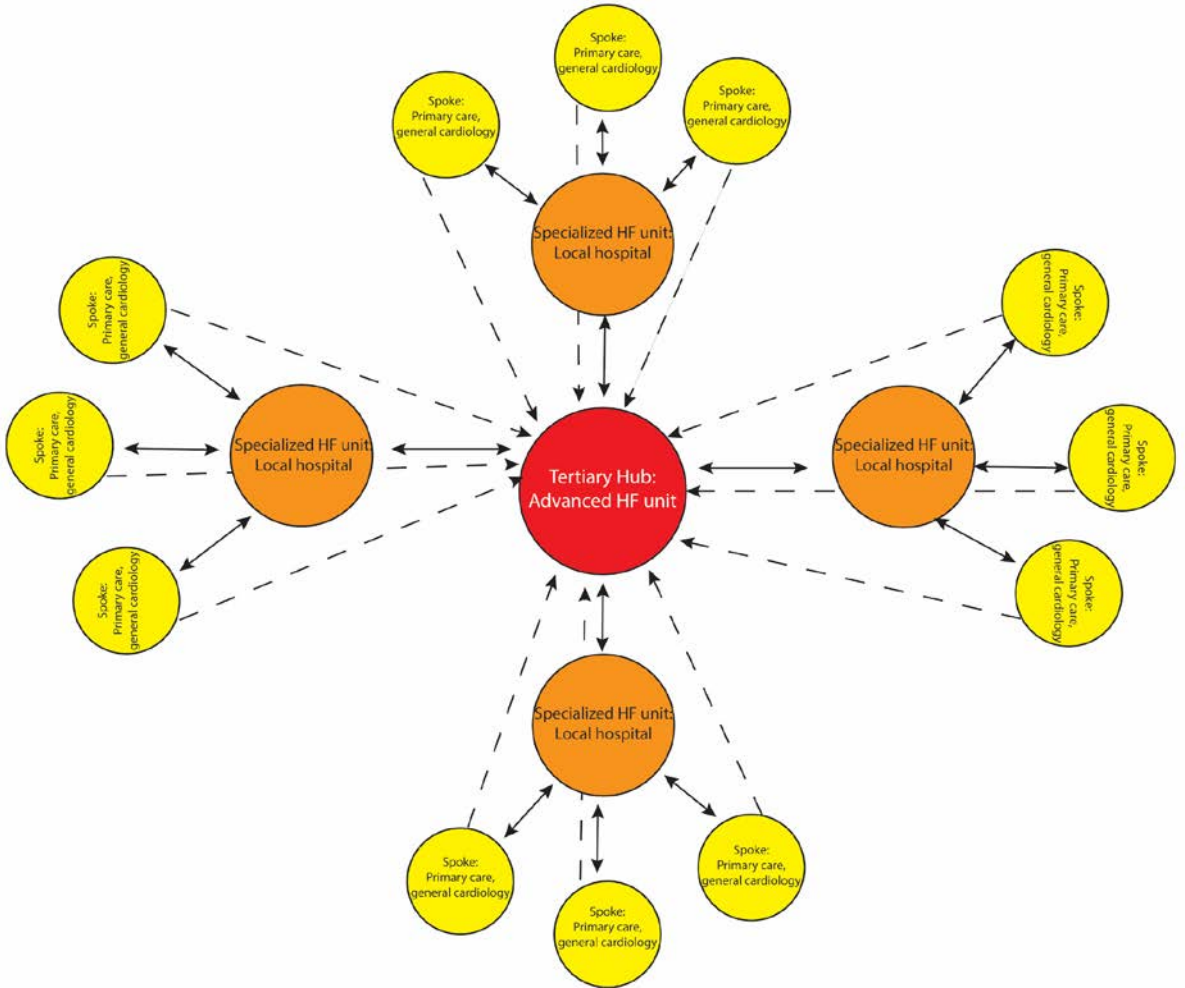
*>75 years if good functional status apart from HF (mono-organ disease)
**e.g., untreatable cancer, dementia, severe COPD

Figure 2.

Spoke: Community heart failure units	Specialized heart failure unit	Tertiary Hub: Advanced heart failure unit
• Primary care provider • General cardiologist • Day-to-day management of heart failure patient • Education • Patient triage and timely access to care	• Intermediate heart failure care • Multidisciplinary team • Heart failure knowledge and expertise • Patient education programs • Training of referring physicians/primary care • Access to cardiac diagnostics • Pharmacologic assessment, optimization and titration of evidence based therapies • Evaluation/implantation of device therapies (e.g., ICD, CRT) • Interventional cardiology • Cardiac surgery • Short-term mechanical circulation support • Risk factor assessment • Specialist consultation • Access to clinical trials	• Community and specialized services, plus: • Access to highly specialized care providers • Advanced diagnostics and interventions (e.g., mechanical circulatory support, transplant) • Provide mentorship to community hub



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