

Advanced heart failure: from definitions to therapeutic options

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Advanced heart failure (AHF) represents an ominous stage of heart failure (HF), where the expected prognosis remains poor regardless of the improvement in medical knowledge. In this review, we summarize the definition, prognosis, pathophysiology, and clinical/therapeutic management of the disease, focusing on the fast and timely referral of the patient to the AHF facilities. We provide an insight of the diagnostic and therapeutic ‘work up’ performed in an Italian AHF hub, implying a deep phenotypical patients characterization in order to evaluate candidacy to the therapeutic gold standards as heart transplantation (HTx) and left ventricular assist device (LVAD).

Definition

‘Advanced’, ‘refractory’, and ‘end-stage’ heart failure (HF) are all interchangeable terms, reflecting patients who should be evaluated for advanced heart failure (AHF) therapies, encompassing cardiac transplantation, long-term mechanical circulatory support (MCS), and palliative therapies.¹

Since treatments are limited, morbidity is typically progressive and survival is often short, deep characterization, and prompt patient identification are paramount. Nevertheless, no unique definition of AHF is available. In fact, the definitions adopted by the main HF organizations focus on marked HF symptoms interfering with daily life and recurrent hospitalizations, underscoring the need for an optimized medical therapy.¹ Differentiating severity of symptoms between groups of patients is not a simple task. The New York Heart Association classification (NYHA) has been widely used to categorize the severity of symptoms in patients with HF. Nevertheless, the inter- and intra-observer variability in the NYHA class have been shown to be large and validity and reproducibility to be low. Moreover, the NYHA class has been found to correlate poorly with objective measures of cardiac function, such as peak oxygen consumption and 6-minute walk distances,² often required to confirm the diagnosis of AHF.

On the other hand, hospitalizations for HF are being replaced by outpatient visits, with infusions of loop diuretics and/or other vasoactive medications, reducing the effective chance of identifying advanced patients.¹

Therefore, no single event or parameter alone can define AHF. Rather, a pattern of clinical characteristics should suggest that a patient has become refractory to traditional therapies, favouring referral to an AHF specialist (*Table 1*).

This concept brought to the 2018 position statement definition of AHF, subsequently adopted by the European Society of Cardiology (ESC) and the American Heart Association (AHA) in the guidelines of HF. In order to define AHF, all these criteria must be present despite optimal guideline-directed treatment:

1. Severe and persistent symptoms of HF (NYHA class III [advanced] or IV)
2. Severe cardiac dysfunction defined by ≥ 1 of these:
 - Left Ventricular Ejection Fraction (LVEF) $\leq 30\%$
 - Isolated RV failure
 - Non-operable severe valve abnormalities
 - Non-operable severe congenital heart disease
 - LVEF $\geq 40\%$, elevated natriuretic peptide levels, and evidence of significant diastolic dysfunction
3. Hospitalizations or unplanned visits in the past 12 months for episodes of:

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Table 1 Main indicators of advanced heart failure/element to define advanced heart failure/trigger for referral

	Heart Failure Association ¹	American College of Cardiology/American Heart Association ²
NYHA class	III (advanced)/IV	III-IV
pVO ₂	<12 to 14 mL/kg/min	<14 mL/kg/min/ < 50% predicted
6 MWT	<300 m	<300 m
Hospitalization	>1 unplanned visit or hospitalization in the last 12 months: *Congestion requiring high-dose intravenous diuretics or diuretic combinations *Low output requiring inotropes or vasoactive medications *Malignant arrhythmias	≥2 HF admissions in 12 months ≥2 unscheduled visits (e.g. ED or clinic) in 12 months
Arrhythmia	>1	Recurrent refractory ventricular tachyarrhythmias; frequent ICD shocks
Echocardiography	LVEF ≤30%, isolated RV failure, non-operable severe valve abnormalities or congenital abnormalities or data of severe diastolic dysfunction or LV structural abnormalities according to the ESC definition of HFpEF and HfmrEF	LVEF < 30%
BNP/NTProBNP	Persistently high (or increasing) BNP or NTproBNP values	Persistently elevated natriuretic peptides
End-organ damage	Liver/Kidney dysfunction/Cardiac Cachexia	Progressive deterioration in renal or hepatic function/Cardiac Cachexia
Pulmonary hypertension Intolerance or down-titration of medical therapy	Type 2 Pulmonary hypertension Intolerant of optimal dose of any HF drug	Pulmonary hypertension Intolerance to RAASi because of hypotension or worsening renal function Intolerance to beta-blockers as a result of worsening HF or hypotension
Diuretics	Increasing diuretic Requirement	Recent need to escalate diuretics to maintain volume status, often reaching daily furosemide equivalent dose >160 mg/d or use of supplemental metolazone therapy
Hypotension	Systolic blood pressure < 90 mmHg	Frequent systolic blood pressure < 90 mmHg
Hyponatraemia	Present	Serum sodium, < 134 mEq/L
Predicted 1-year mortality	MAGGIC predicted survival ≤80% at 1 year SHFM predicted survival ≤80% at 1 year	>20% according to HF survival models (MAGGIC/SHFM).

- Congestion requiring high-dose intravenous diuretics or diuretic combinations
 - Low output requiring inotropes or vasoactive medications
 - Malignant arrhythmias
4. Severe impairment of exercise capacity with inability to exercise or low 6-minute walk test distance (<300 m) or peak VO₂ (<12-14 mL/kg/min) estimated to be of cardiac origin.

Criteria 1 and 4 can be met in patients with cardiac dysfunction (as described in criterion 2) but who also have substantial limitations as a result of other conditions (e.g. severe pulmonary disease, non-cardiac cirrhosis, renal disease). The therapeutic options for these patients may be more limited.¹⁻³

Epidemiology

HF is a global pandemic, estimated to affect 15 million European adults with an incidence ranging from 3/1000 to 5/1000 person-years.³ Although guideline-directed

medical therapies (GDMT) are improving the outcome, patients may still progress to an advanced stage.

The prevalence of AHF remains an epidemiological challenge considering the low incidence of the condition and the absence of a unique definition. Furthermore, there's no epidemiologic study focused only on AHF. However, patients with AHF are estimated as 1-10% of the overall HF population and their prevalence is increasing due to the growing number of patients with HF and the improvement of survival provided by GDMT.⁴

More data regarding AHF prognosis is available. According to the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial, stage D patients treated medically experienced a 75% chance of mortality at 1 year, while no patient survived the 2 years follow-up.⁵ Features predicting an overt worse outcome in this peculiar group of patients are a very low ejection fraction (EF, lower than 25-30%), right ventricular dysfunction regardless EF and comorbidities including pulmonary disease and liver and kidney dysfunction.¹

Physiopathology

The assessment of left ventricular systolic and diastolic pump flow properties is paramount to understand the progression of HF, the effects of drugs recommended, and the need for AHF therapies.

In the most frequent model of disease progression, a patient with structural disorders (Stage B of the AHA/ACC classification) presents a reduction in EF due primarily to an increase in end-diastolic volume (EDV) despite a generally normal stroke volume (SV). Recommended therapies in this stage focus on preventing EDV growing and favouring reverse remodelling (ACE inhibitors, Beta-blockers, mineral receptor antagonists). Patients with symptoms of HF (Stage C of the AHA/ACC classification) present an overt elevation of EDV with rising left ventricular end-diastolic pressure (EDP) and subsequently pulmonary pressures, progressing to right heart dysfunction, and systemic venous congestion, explaining the advancing exercise limitation. The milestone of this stage relies on diuretics, able to reduce circulating volumes. Nevertheless, in the acute phase, selected patients may benefit from the use of vasodilators, low-dose dopamine, or ultrafiltration (UF), varying with the clinical presentation.¹ The chronic therapy of patients symptomatic for HF can be improved with the addition of drugs favouring cardiac remodelling and haemodynamics. Sacubitril/valsartan, for example, has been shown to reduce filling and pulmonary pressures also in patients with severe cardiac dysfunction.⁶ Left ventricular wedge pressure reduction is documented after introducing SGLT2i in HF treatment.⁷ The main feature prevailing in patients with AHF (stage D of the AHA/ACC classification) is the reduction of SV, often accompanied by further LV dilatation, features progressing with the

continuum of the disease and frequently associated with mitral regurgitation, which exacerbates the volume overload, ventricle dilatation, and reduction on SV. This pattern explains the low efficacy of GDMT and diuretics on this phenotype, justifying the use of advanced therapies such as inotropes, MCS or heart transplant (HTx), when possible (Figure 1).^{3,8}

Clinical management

The first step in approaching AHF is the prompt referral of patients 'at risk' to the AHF centre. The most recent ESC guidelines focus on the 'triage of HF', in order to provide timely referral and adequate therapies. NYHA II patients with 'red flags' (Table 1) or NYHA III/IV patients, despite optimal medical therapy, should be at least 'discussed' with the AHF specialists.³ This concept is stressed in the guidelines and the position statements, since a late referral could modify the disease trajectory, allowing the development of irreversible end-organ damage, right ventricle dysfunction, pulmonary hypertension, or cardiac cachexia, that could represent 'high-risk features' or contraindication towards advanced therapies as MCS or HTx.

With this landscape in mind, many prognostic stratification tools have been created. Nevertheless, the assessment of prognosis is particularly challenging for HF. The clinical course, in fact, varies dramatically across the spectrum of disease severity and is relatively unpredictable for individual patients, being exacerbated by the contrast between sudden death and congestive symptoms with progressive pump failure. Moreover, several events



Figure 1 PV loops (created with PVLoops LLC) referring to the AHA-ACC stages of heart failure. On the X coordinate: volume, on the Y coordinate: pressure. Stage A: preserved ejection fraction, normal end-diastolic volumes, filling pressure, and stroke volume. Stage B: left ventricle dysfunction and dilatation with preserved filling pressures and stroke volume (Frank-Starling adaptation). Stage C: symptoms and signs of heart failure, associated with reduced ejection fraction, increased end-diastolic volume, and filling pressure, yet stroke volume is only mildly reduced or preserved. Stage D: advanced heart failure, symptoms and signs of heart failure, associated with reduced ejection fraction, increased end-diastolic volume, and filling pressure. The stroke volume is reduced.

can represent an ‘inflection point’ in the overall trajectory, changing considerably the outcome of the disease.

Among the various scores proposed (SHFS score or Seattle Heart Failure Mode, HFSS or Heart Failure Survival Score, MECKI or Metabolic Exercise Cardiac Kidney Index), the MAGGIC predictive model (Meta-Analysis Global Group in Chronic Heart Failure) may be quite useful given its derivation and validation across multiple clinical trials and cohorts.¹

Since there are no data to support specific cut-offs for referral to an AHF centre, although risk scores and red flags may be clinically relevant, patient recognition remains a crucial phase. No single parameter or parameter combination can fulfil the task of precise profiling of AHF. Yet, a risk score threshold of mortality higher than 20% in a year is considered valuable.¹

The interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles are a commonly used descriptor of disease severity in patients with AHF, being used to define candidate selection and timing for durable MCS, but also performing in prognosis estimation,

with data encompassing a 1-year horizon in ambulatory AHF patients.⁹ Since this classification was born to identify timing for MCS implant, it can be adopted with patients with HF with reduced EF (HF_rEF) in patients without contraindication to mechanical devices.

Once a patient fulfils the definition of AHF, with the limitation provided, a deep characterization needs to be performed, in order primarily to exclude reversible cause of HF, beyond the scope of this document, and provide a clinical picture of the patient. Combining laboratory data, electrocardiography, echocardiography, functional capacity when possible and right heart catheterization, the AHF facility has to provide a medical answer to the need of the patient (Figure 2).

Therapeutic management of AHF

Therapies providing prognostic benefits in AHF patients are HTx and long-term MCS. However, when the clinical

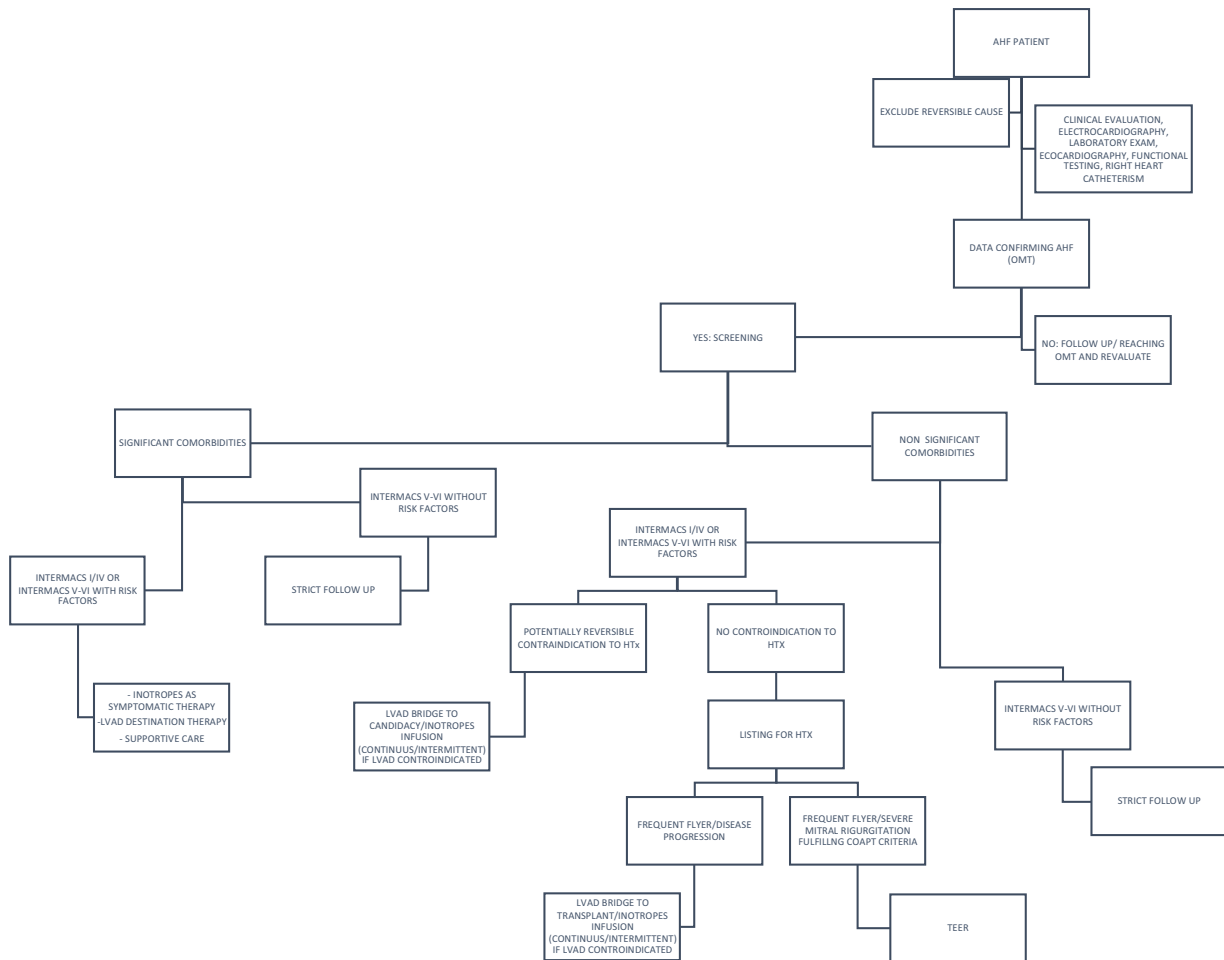


Figure 2 Advanced heart failure (“Microsoft PowerPoint” function): from definition to therapy in the ‘De Gasperis Cardio Center’, Ospedale Niguarda Ca’ Granda. AHF, advanced heart failure; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support profiles; LVAD, left ventricle assist device; OMT, optimal medical therapy; TEER, transcatheter edge-to-edge mitral valve repair. Risk factors considered: recurrent hospitalization, progressive end-organ failure, refractory congestion, pulmonary hypertension (Type 2), inability to perform cardiopulmonary exercise test, or peak oxygen consumption <12 mL/min/kg or <50% of expected value.⁴

condition deteriorates or end-organ damage prevails, short-term therapies (including pharmacological therapy, renal replacement therapy, and short-term MCS) may be needed, until prognostic therapies become available or feasible.

Short-term management

A. Inotropes and vasopressors

Inotropes maintain an adequate cardiac output and reduce filling pressures by enhancing cardiac contractility and, in some cases, allowing vasodilatation, representing a potentially useful strategy to improve haemodynamics and end-organ function in AHF. However, their prognostic benefit is controversial and their routine use remains contraindicated.¹ Nevertheless, selected patients can benefit from intravenous (IV) inotropes as a bridge to temporary MCS, long-term MCS, or HTx and as short-term therapy when low cardiac output and evidence of end-organ dysfunction prevail.¹⁰ Moreover, continuous IV inotropes may be considered as a palliative measure for patients without other advanced treatment options.

Levosimendan intermittent infusion deserves a separate discussion. In the last decade, this calcium sensitizer has gained popularity because of its pharmacokinetic. Producing a pharmacologically active metabolite, the drug effect lasts beyond the infusion period. Several clinical studies indicate how the administration of intermittent intravenous infusions of Levosimendan reduces hospitalization and mortality rates in patients with AHF.¹¹ However, none of those trials were designed or powered to provide conclusive insights regarding this scenario. The ongoing LeODOR trial (NCT03437226) will assess the efficacy and safety of repetitive levosimendan infusion provided for 12 weeks in AHF patients. Indirect insight on inotropes use in AHF is provided by the experience built on Omecamtiv Mecarbil, an oral selective cardiac myosin activator, evaluated in chronic HFrEF in a phase 3 trial (GALACTIC-HF) and demonstrating a significant reduction of the composite endpoint of HF event or death from CV causes.¹² Among the patients involved, the group with baseline LVEF $\leq 22\%$ had the greatest relative risk reduction, with a consistent benefit in the subgroup of patients with NYHA class III or IV. Notably, 2258 patients (27%) who met the specified criteria for severe HF (NYHA III-IV, LVEF $\leq 30\%$, and hospitalization for HF within the previous 6 months) experienced a significant reduction of the primary endpoint, which was not demonstrated in patients without severe HF.¹² Given these meaningful results, Omecamtiv Mecarbil has been strongly suggested as an important component of advanced HFrEF treatment.

B. Diuretics and renal replacement therapy

Most HF hospitalizations are due to signs and symptoms of fluid overload. Congestion is strictly connected to kidney dysfunction (cardiorenal syndrome) and loop diuretic resistance which often characterize the clinical course of patients with AHF. In these situations, up-titration of oral loop diuretics should represent the first therapeutic option. Planned ambulatory intravenous administration of loop diuretics may help in maintaining fluid balance and, in cases of inadequate responses, home administration

of intravenous loop diuretics may be suggested. Concomitant administration of thiazide diuretics or metolazone is used as an adjuvant therapy to overcome the braking phenomenon. However, no evidence from clinical trials exists to guide this practice and the risk of worsening renal function or electrolyte disorders, namely, hypokalaemia and hyponatraemia, must be considered. Interestingly, the ADVOR trial recently demonstrated that the addition of acetazolamide to loop diuretic therapy in patients with acute decompensated heart failure resulted in a greater incidence of successful decongestion.¹³ A further novelty could be represented by vasopressin receptor antagonists. As advanced HF is typically characterized by inappropriately high levels of arginine vasopressin, bringing to plasma expansion and dilutional hyponatraemia, the selective V2 receptor antagonist tolvaptan was suggested as a further decongestive weapon. In pre-clinical HF models, the novel dual-acting vasopressin V1a/V2 receptor antagonist pexavaptan showed a better haemodynamic effect compared with tolvaptan, including augmentation of cardiac output and cardiac index and reduction in total peripheral resistance.¹⁴ The first clinical results will soon be available. UF might be an alternative to loop diuretic administration and it may be considered in patients who develop diuretic resistance. Its efficacy is based on the removal of isotonic fluid which occur without direct activation of the renin-angiotensin-aldosterone system if fluid removal rates do not exceed capillary refill. Despite initial safety concerns, UF is associated with greater weight reduction and volume depletion and with shorter hospitalizations when patients are admitted to the hospital.¹⁵ Rates of UF >250 mL/h are not recommended and patients with right HF usually tolerate lower rates. Finally, peritoneal dialysis might be an at-home option for patients with refractory heart failure, cardiorenal syndrome, and fluid overload. In this technique of dialysis, the removal of sodium and water occurs because of the osmotic pressure gradient between the hypertonic dialysate and the hypotonic peritoneal capillary blood. Peritoneal dialysis has a role both in patients with concomitant HF with and without advanced CKD (Stages I-IV) in whom peritoneal dialysis is used as a UF strategy and in those with HF and end-stage renal disease in whom peritoneal dialysis is the renal replacement therapy of choice (CKD Stage V). Compared with haemodialysis, it offers newsworthy advantages, including haemodynamic stability and less inflammation. This strategy can lead to weight loss and a better NYHA classification and quality of life, reducing the length of in-hospital stay. Future studies should determine if peritoneal dialysis is associated with improved survival.

C. Temporary mechanical circulatory support (T-MCS)

Among patients with AHF, short-term MCS may be indicated in the setting of cardiogenic shock (CS), where growing emphasis is being placed on early and aggressive treatment. Several percutaneous and paracorporeal devices are available and may play an important role as a bridge to recovery, a bridge to decision, or a bridge to heart replacement therapy. The specific device chosen largely depends upon the aetiology of CS, the patient's unique physiology, and the cardiac output augmentation required.

C1. Intra-aortic balloon pump

The intra-aortic balloon pump (IABP) is a percutaneously implanted catheter-based balloon that is positioned in the aorta between the left subclavian artery and the renal arteries where inflates during diastole and deflates during systole, augmenting coronary perfusion and myocardial oxygen supply while reducing left ventricular afterload. Its contribution to cardiac output is small, merely 0.5 L/min by some approximations. Because of the easiness of implantation and the low rate of complications IABP has gained widespread use, particularly in the setting of acute ischaemic heart disease, and for protective support during high-risk percutaneous coronary intervention. However, a randomized trial failed to demonstrate benefit on mortality in the setting of acute myocardial infarction.¹⁶ IABP may also be used to provide mechanical support to patients with CS prior to LVAD implantation. A small single-centre study 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.¹⁷ The Altshock-2 trial will provide evidence on whether IABP should be implanted early in acute decompensated HF (ADHF)-CS patients to improve their clinical outcome (NCT04369573).

C2. Impella ventricular support systems (Abiomed Inc., Danvers, MA, USA)

Impella microaxial flow device can be placed percutaneously via arterial vascular access across the aortic valve, where it draws blood from the left ventricular and ejects into the ascending aorta. In this way, it unloads the left ventricle, improving haemodynamics combined with decreasing pulmonary capillary wedge pressure and increasing coronary artery flow. Impella is manufactured in three versions: 2.5 device (12Fr, maximum flow 2.5 L/min), CP device (14Fr, maximum flow 2-4 L/min), and 5.0 device (21Fr, maximum flow 5 L/min). Impella 5.0 is not fully percutaneous and requires a surgical procedure to insert a 21Fr catheter in the femoral artery. Small-size randomized controlled trials provided inconclusive evidence regarding survival benefits in CS patients treated with Impella compared with those treated to IABP.¹⁸ Notably, Impella has been shown to represent a valuable option for acute right ventricular support or for left ventricular unloading during extracorporeal membrane oxygenation (ECMO).¹⁹

C3. Extracorporeal membrane oxygenation (ECMO)

Venoarterial extracorporeal membrane oxygenation (VA-ECMO) is a cardiopulmonary bypass machine based on a centrifugal blood pump that can produce a flow up to 6 L/min, as well as an oxygenator to provide full respiratory support. ECMO guarantees full systemic circulatory and respiratory support, hence it has been increasingly used in refractory CS as a bridge to heart replacement therapy, bridge to decision, or bridge to recovery. ECMO implantation and management require a dedicated team with expertise in this specific area. Even if the haemodynamic improvements associated with this t-MCS commonly restore end-organ perfusion, VA-ECMO delivers 4-6 L/min of flow to the aorta resulting in increased afterload to the left ventricle. In addition, left

ventricular preload can also increase because of incomplete capture of venous return. Those conditions may result in pulmonary congestion and clinically lead to pulmonary oedema and compromised respiratory function. In these cases, left ventricle can be unloaded with different techniques: medical therapies, percutaneously with Impella or IABP or surgically with the insertion of a vent. Other common complications of VA-ECMO include acute limb ischaemia (in the case of peripheral cannulation), stroke, bleeding, and infection. A recent meta-analysis reported that ECMO provided better survival performance in patients in CS when compared with IABP, while clinical advantage was not observed when ECMO was compared with Impella or TandemHeart.²⁰

C4. Tandem-Heart (Livanova, London, UK)

Tandem-Heart consists of an inflow cannula inserted in the femoral vein with access to the left atrium via trans-septal puncture, an extracorporeal centrifugal flow pump, and an arterial outflow cannula inserted into the femoral artery. In this configuration, Tandem-Heart directly unloads the left atrium which results in decrease in left ventricular filling pressures, volume, and oxygen demand. It provides a cardiac output up to 4 L/min. The need for trans-septal puncture and positioning of the inflow cannula into the left atrium makes implant procedure more complex and longer as compared with other short-term percutaneously implanted devices. Similar to other percutaneous devices, randomized controlled trials have yet to demonstrate a survival benefit.²¹

Long-term management

Long-term AHF therapies are indicated when, despite GDMT, HF progression can no longer be adequately managed, severely affecting the quality of life of patients or compromising end-organ function.

A. Heart transplantation (HTx)

HTx is the gold standard treatment for patients with AHF. Although lacking of controlled clinical trials, HTx demonstrated to provide meaningful improvements in quality of life, functional status, and longevity if compared with conventional therapy.¹ Datasets from the International Society of Heart and Lung Transplantation document how the median survival of adult transplant recipients is now higher than 12 years,²² a significant result if compared with the median survival of patients with stage D HF, usually lower than 2 years. Careful patient selection remains the standard for achieving satisfactory post-transplant outcomes.

Once AHF has been confirmed and reversible causes or significant comorbidities excluded, patients' prognosis should be precisely estimated. In fact, the greatest survival benefit is achieved when the predicted mortality risk is higher, provided that end-organ function is preserved.

Treating patient with the best long-standing prognosis is paramount, since the donor allocation programmes have to face a scarce organ supply, with HTx being a limited resource. In Italy, the National Transplantation Centre recently approved a major revision of the heart allocation policy intended to decrease waitlist mortality, particularly

Table 2 The updated Italian National Transplantation Center Heart Allocation System active since 09 March 2020

Status	Inclusion Criteria
1: National Emergency ^{a,b}	<p>Organs are allocated throughout the national territory.</p> <p>Allocation of blood group O donor heart is allowed for recipients of type O, A, B, AB, while group A and B donor heart are allowed for AB recipients.</p> <ul style="list-style-type: none"> • Patients needing short time extracorporeal mechanical circulatory support (VA-ECMO) • TAH or Biventricular EXCOR with irreversible complications • LVAD with at least one of these complications: <ul style="list-style-type: none"> > Untreatable or recurrent pump thrombosis > Driveline deep infection > Other device failures
2: Macro-area Urgency ^{a,c}	<p>Organs are allocated throughout the macro-area territory.</p> <p>Allocation of blood group O donor hearts is not allowed for recipients belonging to groups A and AB.</p> <p><i>Hospitalized patients with contraindication to LVAD implantation and at least one:</i></p> <ul style="list-style-type: none"> • INTERMACs 3 patients with documented dependence from temporary mechanical circulatory support (IABP or Impella) or IV continuous inotropes infusion for more than 7 days • Arrhythmic storm unsuitable for ablation (more than 3 arrhythmic events in 14 days in spite of optimized anti-arrhythmic therapy with normal electrolyte balance) • Adult patients with congenital heart disease, MELD XI score 10-18 almost one of the following characteristic: <ul style="list-style-type: none"> > Ascites, protein losing enteropathy, plastic bronchitis, cyanosis, refractory arrhythmias <p><i>Patients with MCS:</i></p> <ul style="list-style-type: none"> • Biventricular EXCOR implanted >3 months before (contraindication to LVAD and preserved end-organ function) • LVAD with at least one or two of the following features: <ul style="list-style-type: none"> > Previous resolved pump thrombosis, severe aortic regurgitation, HF requiring high dose of furosemide (≥ 100 mg per day) or haemodynamic documentation of insufficient LV unloading, gastrointestinal bleeding not controlled with medical or endoscopic therapy, chronic driveline infection resistant to antibiotic therapy, PRA $\geq 95\%$ <p><i>Uncomplicated LVAD (Grace Period)</i></p> <ul style="list-style-type: none"> • ≤ 65 years old patients • ≥ 12 months on HT waiting list • LVAD implantation ≥ 18 months
3: Ordinary list	All other patients respect the listing criteria

LVAD, left ventricular assist device; HF, heart failure; PRA, panel reactive antibody; TAH, total artificial heart; VA-ECMO, venoarterial extracorporeal membrane oxygenation.

^aIn order to reach status 1 (National Emergency) or status 2 (macro area urgency), patient has to be hospitalized. The only exception allowed regards the so-called grace period: every 12 month, LVAD patients with certain features can be upgraded in status 2 for 30 days.

^bProvided low cardiac output status before VA-ECMO implantation and contraindication to LVAD.

^cHeart Transplant Centres are geographically divided into macro area where donor allocation is managed in status 2 (macro-area urgency).

for the sickest candidates, favouring organ provision to the patients with the greatest need and improving equitable distribution of donor hearts (Table 2).

Multiorgan transplantation remains uncommon and reserved only for highly selected candidates.

In case of transplantation, patients bear the risks of graft rejection and the side effects of immunosuppression (e.g. infections, antibody-mediated rejection, cardiac allograft vasculopathy, late graft dysfunction, malignancy, renal dysfunction, hypertension, diabetes mellitus).²²

Lastly, in 2022, the first patient affected by AHF, previously judged unsuitable for standard management, has received a heart from a genetically modified pig source animal. Although the patient died on day 49 after transplantation, because of uncertain causes, this may represent the first step to an extraordinary scientific progress.²³

B. Left ventricular assist device (LVAD)

Long-term MCS is a valid alternative in patients non-eligible for HTx or in those deteriorating while awaiting HTx. MCS

implantation is burdened by high costs and adverse events, limiting its use and requiring restrictive clinical criteria as well.¹ However, LVAD therapy has evolved rapidly in recent years and the latest generation of devices has improved durability, reduced surgical and haemocompatibility-related complications, and improved patient survival. The most recent device to gain Food and Drug Administration approval for bridge-to-transplant and destination therapy indications is the HeartMate 3 (Abbott, Chicago, Illinois) LVAD. This fully magnetically levitated centrifugal pump was engineered to improve haemocompatibility, reduce stasis, and prolong durability. In the MOMENTUM trial, HeartMate 3 was shown to be non-inferior to HeartMate 2 in terms of survival and reduction in hospitalizations, with a significantly lower risk of pump replacement because of pump thrombosis. The incidence of all bleeding events, thromboembolism and driveline infection remained similar to the older devices.²⁴ Current 2-year survival rates in patients receiving the latest continuous flow LVAD are comparable to those after HTx, with survival rates reported of 80% at 1 year and 70% at 2 years.¹

Nevertheless, the main clinical challenge regarding LVAD implantation remains the selection of the optimal surgical timeframe. The INTERMACs profiles were created to classify potential candidates for MCS for disease severity, suggesting a possible surgical timing. Selected INTERMACs 1-2-3 patients should be considered for MCS over a short period of time (hours, days, or weeks for INTERMACs 3 patients). A different point needs to be made for ambulatory AHF patients. The ROADMAP trial demonstrated the role of LVAD implantation in an INTERMACs 4-7 population. Non-inotrope-dependent patients improved functional capacity and quality of life, albeit with concomitant adverse haemocompatibility events, especially during the first after implantation year. Delayed implantation in this cohort did not increase mortality if compared with the original LVAD implantation group.²⁵

No firm indication exists regarding patient selection and surgical timing for LVAD implantation. INTERMACs profiles are insufficient to quantify the patient's risk and prognosis and countless factors must be taken into consideration, including end-organ function, age, sex, frailty, and need for concomitant procedures. The ongoing Early-VAD (NCT02387112) and Swedish evaluation of LVAD (SweVAD) (NCT02592499) trials will provide answer to this unmet need.

The decision pathway leading to HTx or LVAD is never straightforward and is unique for each patient. Eligibility may change even over time, in a different manner from patient to patients.

Factors patient unrelated, such as time on HTx waiting list, centre's surgical experience, resources and policies can influence decision-making, surgical timing, and therapeutic strategies.

C. Total artificial heart (TAH)

TAH is a form of MCS where the patient's native ventricles and valves are explanted to be replaced by a pneumatically powered artificial heart. Due to the shortage of organ donation and the contraindications limiting LVAD implantation (e.g. right ventricular failure), TAH therapy was initially looked over with enthusiasm, allowing the management of end-stage biventricular heart failure. However, the adverse event rate for TAH patients exceeds the one of patients treated with LVAD alone.²⁶

Great hope has been placed in the CARMAT TAH (C-TAH). This device has three features that allow a physiological simulation, being a masterpiece of biomedical engineering: it is blood-compatible for the use of bovine pericardium, it is pulsatile because of hydraulic pumps mimicking systole and diastole and it is capable of self-regulating towards the physiological needs of the patient.

Even if the C-TAH appears to simulate heart physiology, ongoing clinical trials will clarify the effective advantages of this device.

Conclusion

AHF is characterized by refractory severe HF symptoms and frequent episodes of decompensation despite the attempts of optimizing GDMT.

Selected patients may be eligible for advanced treatment strategies such as MCS and HTx, the first step being the prompt referral of patients 'at risk' to the AHF centre.

The most recent ESC guidelines focus on the 'triage of HF', in order to provide timely referral and adequate therapies.

For patients who will not be candidates for long-term AHF therapies such as LVAD or HTx, a palliative strategy to reduce symptoms, improve quality of life, and reduce the burden of hospitalization should be emphasized.

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Data availability

The manuscript is a review of the available published data and of our Hospital Department experience. Reference are provided as follows.

References

1. Crespo-Leiro MG, Metra M, Lund LH, Milicic D, Costanzo MR, Filippatos G et al. Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2018;**20**:1505-1535.
2. Thibodeau JT, Mishkin JD, Patel PC, Mammen PPA, Markham DW, Drazner MH. IIIB or not IIIB: a previously unanswered question. *J Cardiac Fail* 2012;**18**:367-372.
3. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;**42**:3599-3726. Erratum in: *Eur Heart J*. 2021 Oct 14.
4. Dunlay SM, Roger VL, Killian JM, Weston SA, Schulte PJ, Subramaniam AV et al. Advanced heart failure epidemiology and outcomes: a population-based study. *JACC Heart Fail* 2021;**9**:722-732.
5. Rose EA, Gelijns AC, Moskowitz AJ, Heitjan DF, Stevenson LW, Dembitsky W et al. Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) Study Group. Long-term use of a left ventricular assist device for end-stage heart failure. *N Engl J Med* 2001;**345**:1435-1443.
6. Gentile P, Cantone R, Perna E, Ammirati E, Varrenti M, D'Angelo L et al. Haemodynamic effects of sacubitril/valsartan in advanced heart failure. *ESC Heart Fail* 2022;**9**:894-904.
7. Omar M, Jensen J, Frederiksen PH, Kistorp C, Videbæk L, Poulsen MK et al. Effect of empagliflozin on hemodynamics in patients with heart failure and reduced ejection fraction. *J Am Coll Cardiol* 2020;**76**:2740-2751.
8. Guglin M, Zucker MJ, Borlaug BA, Breen E, Cleveland J, Johnson MR et al. Evaluation for heart transplantation and LVAD implantation: JACC council perspectives. *J Am Coll Cardiol* 2020;**75**:1471-1487.
9. Kittleson MM, Shah P, Lala A, McLean RC, Pamboukian S, Horstmannshof DA et al. INTERMACS Profiles and outcomes of ambulatory advanced heart failure patients: a report from the REVIVAL Registry. *J Heart Lung Transplant* 2020;**39**:16-26.
10. Gentile P, Marini C, Ammirati E, Perna E, Saponara G, Garascia A et al. Long-term administration of intravenous inotropes in advanced heart failure. *ESC Heart Fail* 2021;**8**:4322-4327.
11. Oliva F, Comin-Colet J, Fedele F, Fruhwald F, Gustafsson F, Kivikko M et al. Repetitive levosimendan treatment in the management of advanced heart failure. *Eur Heart J Suppl* 2018;**20**:i11-i20.
12. Teerlink JR, Diaz R, Felker GM, McMurray JJV, Metra M, Solomon SD et al. Cardiac myosin activation with omecamtiv mecarbil in systolic heart failure. *N Engl J Med* 2021;**384**:105-116.
13. Mullens W, Dauw J, Martens P, Verbrugge FH, Nijst P, Meekers E et al. Acetazolamide in acute decompensated heart failure with volume overload. *N Engl J Med* 2022;**387**:1185-1195.
14. Mondritzki T, Mai TA, Vogel J, Pook E, Wasnaire P, Schmeck C et al. Cardiac output improvement by pecavaptan: a novel dual-acting

- vasopressin V1a/V2 receptor antagonist in experimental heart failure. *Eur J Heart Fail* 2021;**23**:743-750.
15. Costanzo MR, Ronco C, Abraham WT, Agostoni P, Barasch J, Fonarow GC *et al*. Extracorporeal ultrafiltration for fluid overload in heart failure: current status and prospects for further research. *J Am Coll Cardiol* 2017;**69**:2428-2445.
 16. Thiele H, Zeymer U, Neumann FJ, Ferenc M, Olbrich HG, Hausleiter J *et al*. Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med* 2012;**367**:1287-1296.
 17. Seyfarth M, Sibbing D, Bauer I, Fröhlich G, Bott-Flügel L, Byrne R *et al*. A randomized clinical trial to evaluate the safety and efficacy of a percutaneous left ventricular assist device versus intra-aortic balloon pumping for treatment of cardiogenic shock caused by myocardial infarction. *J Am Coll Cardiol* 2008;**52**:1584-1588.
 18. Schrage B, Ibrahim K, Loehn T, Werner N, Sinning JM, Pappalardo F *et al*. Impella support for acute myocardial infarction complicated by cardiogenic shock. *Circulation* 2019;**139**:1249-1258.
 19. Pappalardo F, Schulte C, Pieri M, Schrage B, Contri R, Soeffker G *et al*. Concomitant implantation of Impella® on top of veno-arterial extracorporeal membrane oxygenation may improve survival of patients with cardiogenic shock. *Eur J Heart Fail* 2017;**19**:404-412.
 20. Ouweneel DM, Schotborgh JV, Limpens J, Sjauw KD, Engström AE, Lagrand WK *et al*. Extracorporeal life support during cardiac arrest and cardiogenic shock: a systematic review and meta-analysis. *Intensive Care Med* 2016;**42**:1922-1934.
 21. Burkhoff D, Cohen H, Brunckhorst C, O'Neill WW; TandemHeart Investigators Group. A randomized multicenter clinical study to evaluate the safety and efficacy of the TandemHeart percutaneous ventricular assist device versus conventional therapy with intraaortic balloon pumping for treatment of cardiogenic shock. *Am Heart J* 2006;**152**:469 e1-8.
 22. Mehra MR, Canter CE, Hannan MM, Semigran MJ, Uber PA, Baran DA *et al*. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: a 10-year update. *J Heart Lung Transplant* 2016;**35**:1-23.
 23. Griffith BP, Goerlich CE, Singh AK, Rothblatt M, Lau CL, Shah A *et al*. Genetically modified porcine-to-human cardiac xenotransplantation. *N Engl J Med* 2022;**387**:35-44.
 24. Mehra MR, Uriel N, Naka Y, Cleveland JC Jr, Yuzefpolskaya M, Salerno CT, *et al*. A fully magnetically levitated left ventricular assist device - final report. *N Engl J Med*. 2019; **380**:1618-1627.
 25. Starling RC, Estep JD, Horstmanshof DA, Milano CA, Stehlik J, Shah KB *et al*. Risk assessment and comparative effectiveness of left ventricular assist device and medical management in ambulatory heart failure patients: the ROADMAP study 2-year results. *JACC Heart Fail* 2017;**5**: 518-527.
 26. Arabia FA, Cantor RS, Koehl DA, Kasirajan V, Gregoric I, Moriguchi JD *et al*. Interagency registry for mechanically assisted circulatory support report on the total artificial heart. *J Heart Lung Transplant* 2018;**37**:1304-1312.