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Review

Advanced heart failure: state of the art and future directions

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Abstract

Advanced heart failure is a clinical challenge that requires a pathophysiological-based approach. As the field has been the subject of multiple reviews, the objective of this paper is not to duplicate these publications but rather to offer practical tips for the clinical cardiologist to enable the optimal management of patients with advanced heart failure. Advanced heart failure is defined as a clinical syndrome characterized by severe and persistent symptoms, most commonly with severe ventricular dysfunction, despite optimized medical therapy. This review covers the management of the advanced heart failure patient from pharmacologic therapy with disease-modifying drugs, to the use of electrical therapy devices, percutaneous valve repair and finally to the role of left ventricular assist devices and heart transplantation. The review also explores future directions in the management of advanced heart failure, including translational perspectives for the treatment of this syndrome.

Keywords: advanced heart failure; acutely decompensated heart failure; inotropes; left ventricular assist device; HeartMate 3; heart transplant

1. Introduction

Despite improvements in pharmacological and non-pharmacological treatments for patients with heart failure (HF) with reduced ejection fraction (HFrEF) [1], up to 13% of patients do not respond to conventional approaches, resulting in disease progression to the most advanced stage of HF [2].

Advanced HF (AdvHF) is defined as a clinical syndrome characterized by severe and persistent symptoms, often with severe ventricular dysfunction, despite optimized medical therapy [3]. Acutely decompensated HF, on the other hand, is defined as the appearance of new or worsening signs and symptoms of HF, often leading to hospitalization or presentation to the emergency department. Frequent episodes of acutely decompensated HF are one of the hallmarks of AdvHF. Patients with AdvHF present a management challenge for the clinical cardiologist. For these patients, triage to options including titration of disease-modifying drugs [4], myocardial revascularization, repair of severe mitral or tricuspid valvular insufficiency [5], implantation of a ventricular assist device [6], or heart transplant evaluation [7] requires additional knowledge, skills, and experience beyond that acquired during a fellowship in cardiovascular medicine. To help clinical cardiologists better manage this challenging clinical syndrome, this review summarizes the pathophysiology, diagnosis, and therapeutic options of AdvHF.

2. Definition and diagnostic criteria of AdvHF

AdvHF has a highly unpredictable clinical course, which complicates early diagnosis and timely referral to a third-level center. While in some cases, AdvHF progresses rapidly to cardiogenic shock, in other cases it evolves slowly over time (indolent progressive shock) [8,9]. Therefore, in the most recent definitions of AdvHF, data on functional capacity, quality of life, cardiac structure/function, and biomarkers have been added as essential complements to define AdvHF, even in the presence of apparent clinical stability (Table 1, Ref. [10–12]).

3. Pathophysiology and clinical presentation of AdvHF

Patients with AdvHF manifest a specific hemodynamic profile characterized by high left ventricular filling pressure (resulting in congestion) and low cardiac output (resulting in systemic hypoperfusion) [13]. Orthopnea and elevated jugular venous pressure are typical symptoms and signs of high left ventricular filling pressure [14]. In addition to these "traditional" signs and symptoms, bendopnea (i.e., dyspnea that occurs when a patient leans forward, such as when bending over to tie shoes) is a specific symptom of AdvHF [15]. Conversely, rales, described as pathognomonic of chronic HF, are absent in >80% of patients with AdvHF (with chronically elevated filling pressure due to pulmonary lymphatic vessel compensation) [16]. On the other hand, peripheral edema is generally unrelated to left

Table 1. Definition of AdvHF according to international society guidelines and consensus papers.

AHA/ACC [10]	HFSA [11]	HFA [12]
Two or more episodes of acutely decompensated HF in the last 12 months	Two or more episodes of acutely decompensated HF in the last 12 months	Two or more episodes of acutely decompensated HF in the last 12 months due to pulmonary or systemic congestion, low output state or malignant ventricular arrhythmias
Progressive reduction of renal function	Progressive deterioration in renal and hepatic function	Severe cardiac dysfunction as defined by reduced left ventricular ejection fraction $\leq$30%, isolated right-ventricle failure, or inoperable severe valve diseases
Cardiac cachexia	Severe reduction of exercise capacity as documented by a peak VO_2 $<$14 mL/kg/min (or $<$50% predicted) at cardiopulmonary exercise test or a distance $<$300 m at 6-minute walking-test	Severe reduction of exercise capacity as documented by a peak VO_2 $<$14–12 mL/kg/min at cardiopulmonary exercise test or a distance $<$300 m at 6-minute walking-test estimated to be of cardiac origin
Intolerance to disease-modifying drugs	Intolerance to disease-modifying drugs	NYHA class III–IV
NYHA class III–IV	NYHA class III–IV	Cachexia, liver or renal dysfunction due to HF or type 2 pulmonary hypertension
Hypotension (SBP $<$90 mmHg)	Diuretic refractoriness associated with worsening renal function	
Need of escalated diuretic therapy or addition of metolazone in the last month	Three or more sustained episodes of ventricular tachycardia, ventricular fibrillation or appropriate implantable cardioverter-defibrillator shocks during a 24-hour period	
Three or more sustained episodes of ventricular tachycardia, ventricular fibrillation or appropriate implantable cardioverter-defibrillator shocks during a 24-hour period	Persistent low serum sodium (usually $<$133 mEq/L)	
Persistent low serum sodium (usually $<$133 mEq/L)	Worsening right HF and type II pulmonary hypertension Need for intravenous inotropic therapy for symptomatic relief or to maintain organ perfusion	

Abbreviations: AHA/ACC, American Heart Association/American College of Cardiology; HFSA, Heart Failure Society of America; HFA, Heart Failure Association; HF, Heart Failure; VO_2, Volume of Oxygen; SBP, Systolic Blood Pressure; NYHA, New York Heart Association.

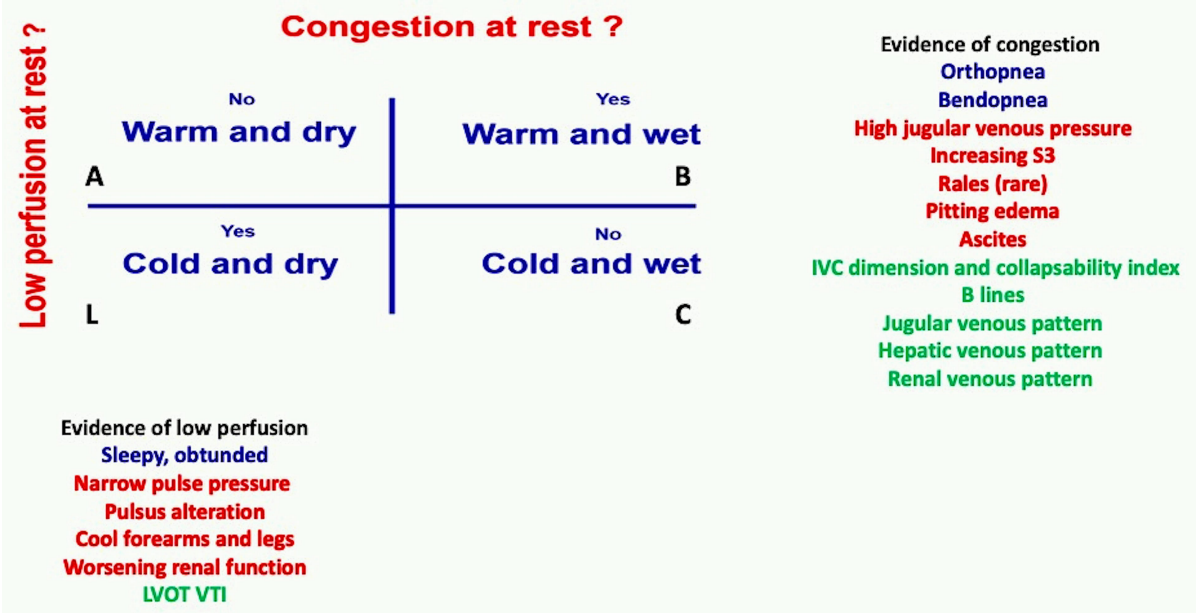

Fig. 1. Clinical (blue), "old" (red), and "new" (green) echocardiographic features of patients with AdvHF according to hemodynamic profile. Abbreviations: LVOT VTI, Left Ventricular Outflow Tract Velocity-Time Integral.

ventricular filling pressure, but rather to increased central venous volume. The most accessible evidence of perfusion is blood pressure, which requires careful auscultation to determine pulse-pressure amplitude. A proportional pulse pressure <25% suggests a low output state (i.e., cardiac index <2.2 L/min/m^2) in patients with AdvHF [17]. This finding requires further confirmation, particularly in elderly patients with less compliant vessels. Altered mental status may be a sign of severely reduced organ perfusion; patients may report somnolence after meals or extreme generalized fatigue and weakness [18,19].

Furthermore, cold forearms and legs, or more specifically cold hands and feet, are present in the low cardiac output syndrome [20]. Finally, a typical symptom of low organ perfusion is the occurrence of symptomatic hypotension following the administration of disease-modifying drugs (even at low doses) [21]. Fig. 1 summarizes the symptoms and signs of the hemodynamic profile of HF. Notably, these hemodynamic profiles are useful not only for diagnosis; but for prognosis as well. In a series of 486 patients with AdvHF, 67% had a B profile (wet and warm), 28% had a C profile (cold and wet), and only 5% were found to be cold and dry. At 1-year follow-up, death and cardiac transplantation rates were twice as high in patients with C profiles than B profiles [22].

4. Referral of patients with AdvHF to an AdvHF center

In view of the potential increase in mortality and morbidity due to late initiation of advanced therapy for AdvHF, any red flags suggesting advanced HF should be identified at every patient encounter. Fortunately, many easily recognized clinical signs and events indicate that a patient with apparent clinical stability has AdvHF. Clinical elements characterizing a particularly poor prognosis are those indicating labile hemodynamic compensation, such as recurrent hospitalizations, intolerance to guideline-directed medical therapy, increasing arrhythmic burden (atrial fibrillation and complex ventricular arrhythmias), and worsening renal and hepatic function. A mnemonic for remembering these elements is "I NEED HELP" [23] (Fig. 2). This acronym is useful for early referral to an AdvHF specialist before the onset of irreversible multiorgan dysfunction precludes candidacy for surgical therapy (i.e., mechanical circulatory support or heart transplantation) [24].

It is essential to note that a HF hospitalization is a sentinel event, and the presence of two or more hospitalizations for HF in the prior 12 months identifies a patient with 1-year mortality >40% [25]. The intolerance to disease-modifying drugs is also associated with a poor prognosis [26,27]. The presence of a burden of complex ventricular tachyarrhythmias (sustained ventricular tachycardias/ventricular fibrillation) with or without appropriate defibrillator shocks also indicates a worrying prognosis [28,29]. The presence of even a single red flag should signal further investigation which may include a cardiopulmonary exercise test and right-heart catheterization [30] as well as referral to an AdvHF center.

5. Pharmacological therapy

Pharmacological treatment of patients with AdvHF is based on guideline-directed medical therapy with disease-modifying drugs, diuretics, and inotropes.

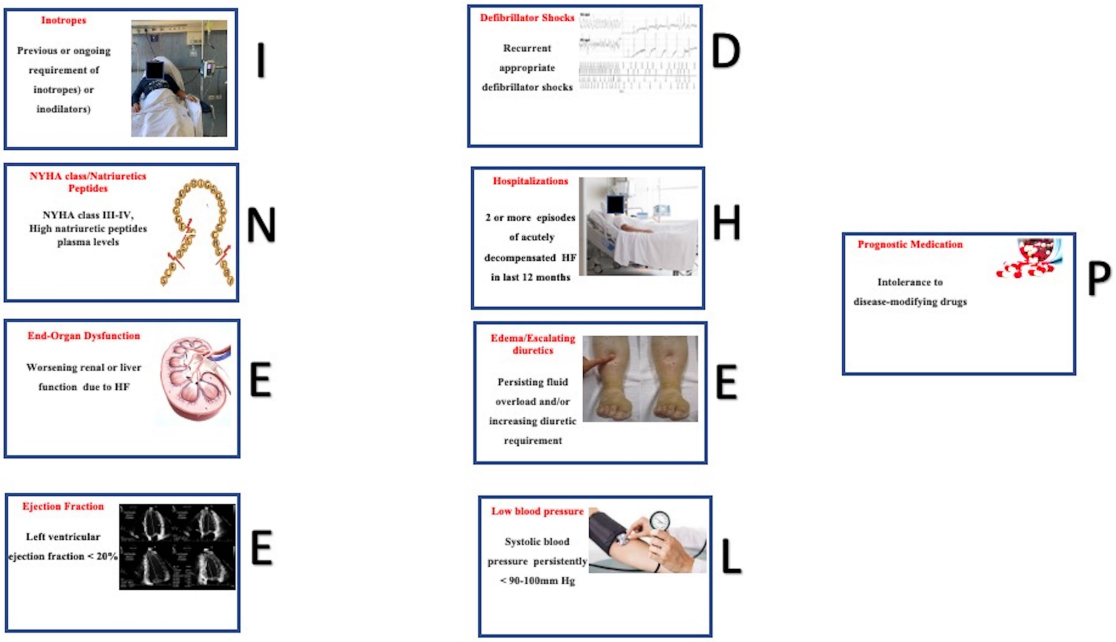

Fig. 2. I NEED HELP acronym to identify patients with AdvHF that should be referred to a tertiary center. Abbreviations: HF, Heart Failure; NYHA, New York Heart Associations.

5.1 Disease-modifying drugs

The use of disease-modifying drugs in patients with AdvHF represents a clinical challenge, due to factors limiting the use of these drugs (e.g., hypotension, renal dysfunction, and electrolyte alterations). This section describes the clinical trial evidence and practical strategies for optimizing disease-modifying drug use in AdvHF.

5.1.1 β-blockers

β-blockers antagonize the hyperactivated sympathetic nervous system in patients with HFrEF [31]. The benefit of β-blockers in patients with HFrEF was shown in several randomized clinical trials that documented reduction in mortality and hospitalizations compared to placebo.

The only trial that enrolled patients with AdvHF is the COPERNICUS trial that enrolled 2289 HF patients with severe reduction of left ventricular ejection fraction (<25%) and symptoms at rest or minimal exertion (NYHA class III–IV) for at least 2 months despite optimized medical therapy that were randomized to carvedilol or placebo [32]. Patients in the carvedilol group had a significant reduction of mortality compared to patients in the placebo group (relative risk reduction 35%, interquartile range (IQR), [19%–48%]).

However, there is no definite evidence on the effect of β-blockers on the quality of life of patients with AdvHF; studies had a small sample size and therefore were not conclusive. Therefore, B-blockers should always be used in conjunction with other disease-modifying drugs.

Based on these data and international society guidelines, we recommend the use of β-blockers in all patients with AdvHF, with a preference for those with more minor hypotensive effects (bisoprolol and sustained-release metoprolol), starting with low doses (bisoprolol 1.25 mg or metoprolol succinate 12.5 mg) and cautious and slow up-titration (50% increase every 2–4 weeks). In patients with AdvHF in whom β-blockers are not tolerated or for whom heart rate (in sinus rhythm) remains over 70 beats per minute on maximum-tolerated β-blockers, ivabradine should be considered [33].

5.1.2 Renin–angiotensin–aldosterone system modulators

Optimizing therapy with drugs that antagonize the renin–angiotensin–aldosterone system (RAAS) is a clinical challenge in patients with AdvHF due to the risk of hypotension, worsening of renal function, and electrolyte abnormalities [34].

Sacubitril–valsartan is widely used not only in patients with HFrEF but also in those with AdvHF, due to improved clinical and hemodynamic outcomes [35,36].

The PARADIGM-HF trial enrolled 8442 patients with HFrEF on optimized medical therapy randomized to sacubitril/valsartan and enalapril. The study was stopped early after a median follow-up of 27 months due to the significant benefit of sacubitril/valsartan (20% reduction in relative risk of cardiovascular mortality and 21% reduction in HF-related hospitalizations) [37].

The LIFE study involving sacubitril/valsartan was found not to be superior compared to valsartan with respect to reducing N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels in patients with AdvHF and there was no difference in a composite clinical end-point (number of days alive out of hospital and without heart failure events)

[38]. However, it was not powered to determine significance for relevant clinical endpoints. Thus, despite the negative results of that trial, we believe that sacubitril–valsartan is a valid therapeutic option in patients with AdvHF. In all patients, we recommend a starting dose of 24/26 mg twice daily or an even lower starting dose of 24/26 mg ½ tab twice daily, then switching to 24/26 mg twice daily. Slow up-titration should be performed in AdvHF patients, with a 50% increase in the daily dose every 2 weeks. Titration of sacubitril/valsartan is likely to be better tolerated than titration of β-blockers, since sacubitril/valsartan offers the acute hemodynamic benefit of afterload reduction in addition to long-term beneficial neurohormonal modulation.

Diuretic therapy may need to be reduced given the natriuretic properties of sacubitril [39,40]. The use of sacubitril/valsartan should be prioritized in patients with low blood pressure over other vasodilator drugs such as nitrates. In cases of intolerance to sacubitril–valsartan, treatment with an angiotensin converting enzyme (ACE) inhibitor or, if not tolerated, an angiotensin receptor blocker (ARB), should be initiated with once daily evening dosing to minimize daytime symptomatic hypotension [41]. In the CONSENSUS and SOLVD trials, even low dose ACE inhibitors resulted in a significant reduction in mortality as well as improvement in. quality of life by reducing symptoms related to hypotension [42,43].

5.1.3 Mineralocorticoid-receptor antagonists

The most effective strategy for complete RAAS inhibition is combining Angiontensin Receptor Neprilysin Inhibitor (ARNI)/ACE inhibitors/ARBs with mineralocorticoid-receptor antagonists [44]. In the RALES trial, even in patients with AdvHF, spironolactone reduce mortality (relative risk 0.70, 95% CI 0.60–0.82; $p < 0.001$) and hospitalization (relative risk 0.65, 95% CI 0.54–0.77; $p < 0.01$) [45]. Furthermore, in this population, the advantage of this treatment was maintained even in patients with renal impairment or mild hyperkalemia [46]. For these reasons, even in the absence of definitive evidence on the effect of these drugs on the improvement of quality of life, we recommend for all patients with AdvHF and serum K^+ <5 mEq/L; the cautious introduction of low doses of spironolactone (12.5 mg) with titration after 2–4 weeks to the target dose of 25 mg daily and periodic checks of potassium levels. If potassium levels are >6 mEq/L after introducing mineralocorticoid receptor–antagonist treatment, we recommend discontinuing all drugs that interact with the RAAS. The development of new medications for the treatment of hyperkalemia (patiromer and ZS9) may optimize RAAS-modifier therapy even in patients with AdvHF [47]. However, little evidence exists to guide the use of potassium binders with hyperkalemia in response to RAAS-modifiers, and the benefit versus the increase in cost and polypharmacy needs to be weighed.

5.1.4 Sodium-glucose cotransporter-2 (SGLT2) inhibitors

This new class of diabetic drugs, with a pleiotropic organ-protective effect at the cardiac and renal levels, reduces HF hospitalizations and has recently been shown to decrease cardiovascular mortality in a randomized clinical trial [48]. In the DAPA-HF trial, use of dapagliflozin was associated with a reduction in the primary end point (a composite end point of cardiovascular mortality and HF hospitalizations), with a 26% relative risk reduction regardless of the presence of diabetes, and a significant reduction in cardiovascular mortality alone [49]. In the EMPEROR-Reduced study [50], use of empagliflozin also resulted in a 25% reduction in the primary end point (cardiovascular death or HF hospitalizations) but no reduction in mortality alone [hazard ratio (HR) 0.92, 95% CI 0.75–1.12].

Both drugs also reduce the progression of chronic kidney disease, a frequent co-morbidity in patients with HF, regardless of the presence of diabetes; and lead to improved quality of life.

While there are no trials targeted at the AdvHF population, we recommend the addition of an SGLT2 inhibitor to RAAS-modifiers and β-blockers if tolerated; based on blood pressure and renal function in an attempt to offer patients the greatest reduction in HF morbidity and mortality.

5.2 Diuretics

Virtually all patients with AdvHF have some degree of chronic congestion and thus need diuretics [51]. High doses of loop diuretics are the gold standard therapy for the treatment of peripheral congestion in patients with AdvHF [52]. However, the use of these drugs may perpetuate the pathophysiological processes responsible for the progression of HF (RAAS hyperactivation, hyperactivation of the sympathetic nervous system) and contribute to diuretic resistance [53]. Both neprilysin inhibitors and SGLT2 inhibitors have diuretic properties and may work to relieve congestion without a detrimental neurohormonal impact. The addition of a thiazide diuretic or metolazone (a thiazide-like diuretics) in accordance with the sequential nephron-blockade strategy, may induce powerful diuresis [54], but increases the risk of hypokalemia (which could be avoided or corrected by adding high doses of aldosterone antagonists). In patients unresponsive to sequential nephron blockade, other treatment strategies are required, as shown in Fig. 3.

5.3 Inotropes

In patients with AdvHF, several inotropic and vasopressor agents with different mechanisms of action (Table 2) may be used as long-term palliative therapies or as a bridging solution to left ventricular assist device (LVAD) implantation and heart transplantation [55].

Because conventional inotropes (β-adrenergic agonists, phosphodiesterase 3 inhibitors) act through an increase in intracellular calcium concentration and hence carry an increased risk of ventricular arrhythmias, peri-

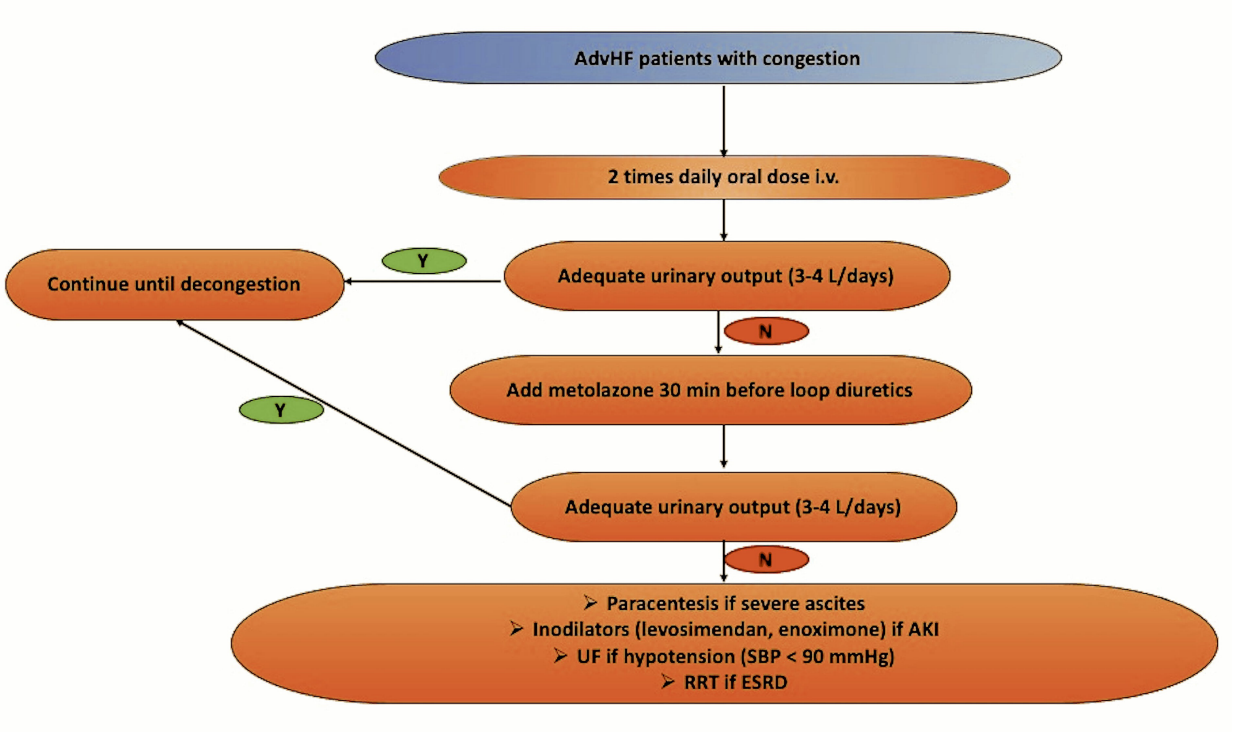

Fig. 3. Algorithm for management of congestion in patients with AdvHF. Abbreviations: UF, Ultrafiltration; AKI, Acute Kidney Injury; RRT, Renal Replacement Therapy; SBP, Systolic Blood Pressure; ESRD, End-Stage Renal Disease.

odic infusion of levosimendan may be a better option for patients with AdvHF [56]. In fact, levosimendan has a mechanism of action that does not result in an increase in intracytoplasmic calcium concentration; it is a calcium-sensitizing drug that selectively increases the affinity of troponin C for calcium in a concentration-dependent manner. In addition, due to the activation of adenosine triphosphate (ATP)-dependent K channels of smooth muscle cells, levosimendan causes systemic and pulmonary vasodilation and activation of ATP-dependent K channels of mitochondria which is responsible for organ protection [57]. Levosimendan has a more prolonged pharmacological action (10–14 days) than other inotropic drugs, due to the long half-life (about 80 hours) of its active metabolite—OR1896. In clinical trials and a single-center study, ambulatory infusion of levosimendan improved functional capacity and quality of life and reduced hospitalizations in outpatients with advanced HFrEF [58,59] without an increase in arrhythmic burden. Moreover, an echocardiographic pilot study showed that 6 hours' infusion of levosimendan increased cardiac index and cardiac output and reduced left atrial pressure and pulmonary pressure in outpatients with AdvHF [60].

For these reasons, we believe that intermittent use of levosimendan is a viable treatment option for some patients with AdvHF, particularly those with a contraindication to LVAD implantation or heart transplantation (destination therapy) or as a bridge to these treatment options. However, levosimendan is not available in the United States. In inotrope-dependent AdvHF patients in the United States, dobutamine, milrinone, and dopamine are most commonly used for palliation or as a bridge to advanced therapies [61].

6. Cardiac electronic device–based therapy

Cardiac implantable electronic device therapy has become an essential therapeutic option for managing both life-threatening ventricular arrhythmias and systolic dysfunction in AdvHF patients [62]. In its broadest application, it includes both devices that prevent sudden cardiac and devices that improve cardiac performance, such as cardiac resynchronization therapy (CRT) or cardiac contractility–modulation therapy (CCM) [63]. Since the use of devices for the prevention of sudden death occurs predominantly in the early stages of HFrEF; and given the fact that AdvHF patients' mortality is essentially related to the progression of HF, rather than sudden death, in the following sections we describe the roles of CRT and CCM in patients with AdvHF.

6.1 CRT

CRT is the treatment of choice for HFrEF patients with left ventricular ejection fraction (LVEF) $<35\%$ and a wide QRS interval [64]. International guidelines recommend CRT in patients with HF, LVEF $<35\%$, who remain symptomatic (NYHA class II–IV) despite optimal medical therapy, and have a left bundle-branch block (LBBB) with a QRS duration >150 ms [65]. Several randomized clinical trials of CRT have been performed involving more than

Table 2. Clinical pharmacology of inotropes and vasopressor use in patients with AdvHF.

Pharmacologic agent	Mechanism of action	Hemodynamic effects	Dose
Dopamine	DR > b1 > a	Increase CO/CI Increase PVR/SVR Increase HR	No bolus dosing Infusion dose: 1–20 g/kg/min
Dobutamine	b1 > b2 > a	Increase CO/CI Reduce PVR/SVR Increase HR	No bolus dosing Infusion dose: 2–20 g/kg/min
Milrinone/Enoximone	PD3 inhibitors	Increase CO/CI Reduce PVR/SVR	Bolus dosing: 20–50 g/kg/min Infusion dose: 0.2–0.75 g/kg/min
Levosimendan	Calcium sensitizer	Increase CO/CI Reduce PVR/SVR	No bolus dosing Infusion dose: 0.05–0.2 g/kg/min
Norepinephrine	a > b1 > b2	Increase CO/CI Increase PVR/SVR	No bolus dosing Infusion dose: 0.1–1 g/kg/min
Epinephrine	a > b1 > b2	Increase CO/CI Increase PVR/SVR Increase HR	No bolus dosing Infusion dose: 0.01–0.2 g/kg/min

Abbreviations: CI, Cardiac Index; CO, Cardiac Output; DR, Dopaminergic Receptors; HR, Heart Rate; PVR, Pulmonary Vascular Resistance; SVR, Systemic Vascular Resistance.

Table 3. Principal characteristic of novel device for transcatheter mitral annuloplasty.

Name of device	Type of device	CE approval	FDA approval	N° of patients in trials	Results
Cardioband	Direct annuloplasty	Yes	No	92	Reduction of degree of mitral regurgitation in 68% of patients with significant improvement in functional status and quality of life
Mitralign	Direct annuloplasty	No	No	71	Reduction of degree of mitral regurgitation in 50% of patients with significant improvement in functional status and quality of life
Carillon	Indirect annuloplasty	Yes	No	278	Reduction of degree of mitral regurgitation in 50% of patients with significant improvement in functional status and quality of life

8500 patients with HFrEF, NYHA class II–IV symptoms, and a QRS >120 ms [66]. These trails clearly demonstrate that CRT reduces mortality and morbidity in HFrEF patients and improves functional capacity, exercise capacity, and quality of life. Irrespective of NYHA class, CRT results in reduced ventricular volumes, increased ejection fraction, and reduced functional mitral regurgitation (also known as reverse remodeling) [67]. These improvements occur most prominently in patients with LBBB and QRS >150 ms, although they can also be seen in patients with left bandle brunch block (LBBB) and QRS duration between 120–149 milliseconds [68]. In contrast, in patients with QRS <130, CRT results in a worse prognosis. The Echo-CRT study, enrolled 809 patients with HFrEF, NYHA class III or IV, a LVEF of 35% or less, a QRS duration of less than 130 msec, and echocardiographic evidence of left ventricular dyssynchrony. This trial was stopped early due to an increased mortality in the CRT group compared to control (11.1% vs. 6.4%; HR 1.81; 95% CI 1.11–2.93; $p = 0.02$) [69].

Based on these data, we recommend CRT in patients with HFrEF NYHA functional class II–IV with left ventricular ejection fraction <35% and left bundle-branch block (or ventricular pacing dependence) on optimized medical therapy. Considering these criteria, only 20%–30% of patients with HFrEF are candidates for CRT, for the other 70% of patients, a novel therapeutic available option is CCM.

6.2 CCM

CCM is an innovative therapy for treating patients with HF. It acts through the delivery of biphasic, long-duration (~20 ms), and relatively high-voltage (~7.5 V) electrical pulses during the absolute refractory period [70].

Table 4. Hemodynamics effects and clinical indications of temporary mechanical circulatory support systems.

Name of device	Type of support	Hemodinamic effects	Indications	Notes
IABP	Minimal hemodynamic support (0.3–0.5 L/min)	↑ CO ↓ LVEDP ↓ PCWP	AHF with low output state, cardiogenic shock, high risk PCI	Can be used without anticoagulation
Impella	Partial (2 L/min) or complete (5.5 L/min) left ventricular support based upon the size of the outflow cannula	↑↑ CO ↓↓ LVEDP ↓↓ PCWP	AHF with low output state, cardiogenic shock, high risk PCI, refractory malignant arrhythmias	Active left ventricular unloading
Tandem Heart	Partial (2 L/min) or complete (5.5 L/min) left ventricular support based upon the size of the outflow cannula	↑↑ CO ↓↓ LVEDP ↓↓ PCWP	AHF with low output state, cardiogenic shock, high risk PCI, refractory malignant arrhythmias	Passive (indirect) left ventricular unloading by decompressing the left atrium Requires septostomy
Impella RP	Partial (2 L/min) or complete (4 L/min) right ventricular support based upon the size of the outflow cannula	↑ MPAP ↓ RAP ↓↓ PCWP	RV failure after cardiac surgery or LVAD placement RV failure associated to malignant ventricular arrhythmias and severe mitral regurgitation	Increase of PCWP Increase of native CO if preserved left ventricular systolic function
Protek Duo	Partial (2 L/min) or complete (4 L/min) right ventricular support based upon the size of the outflow cannula	↑ MPAP ↓ RAP ↓↓ PCWP	RV failure after cardiac surgery or LVAD placement RV failure associated to malignant ventricular arrhythmias, pulmonary hypertension or acute coronary syndrome	Increase of PCWP Increase of native CO if preserved left ventricular systolic function
VA-ECMO	Complete biventricular support (3–7 L/min)	↑↑ CO ↓ RAP ↑↑ LVEDP ↑↑ PCWP	AHF with low output state, cardiogenic shock, refractory malignant arrhythmias, cardiac arrest	May Require strategies for left ventricular unloading (vent)

Abbreviations: CO, Cardiac Output; LVEDP, Left Ventricular End-Diastolic Pressure; PCWP, Pulmonary Capillary Wedge Pressure; RA, Right Atrial; MPAP, Mean Pulmonary Arterial Pressure; AHF, Acute Heart Failure; PCI, Percutaneous Coronary Intervention; RV, Right Ventricle; LVAD, Left Ventricular Assist Device.

As such, CCM does not cause a new contraction. In the short term, electrical stimulation by CCM results in improved calcium handling. In the long term, CCM effects several biochemical and molecular processes, such as reduced expression of fetal genes (overexpressed in the failing myocardium), improved calcium cycling, and ultimately myocardial contraction [71,72]. Randomized clinical trials have shown that CCM can lead to a reduction in hospitalizations and an improvement in functional capacity and quality of life in patients with HF. However, the survival benefit of CCM has not been prospectively elucidated due to short-term follow-up in existing clinical trials.

In 68 patients with previous CCM implantation retrospectively followed for 4.5 years, this therapy resulted in lower mortality rates than predicted by the Seattle Heart Failure Model (SHFM) (14.2% at 5 years compared with the SHFM predicted rate of 27.7%) [73].

In another retrospective single-center study that enrolled 81 patients with CCM, at a mean follow-up of three years, these patients had improvements in ejection fraction, quality of life as measured by the Minnesota Living with Heart Failure questionnaire, and a reduction in symptoms [74]. These patients had lower mortality rates than predicted by the Meta-Analysis Global Group in Chronic Heart Failure scores.

Recent results from the largest published registry to date, CCM-REG25-45, documented survival rates of patients with LVEF <35% to be significantly higher than survival predicted by the SHFM ($p = 0.46$) [75]. Based on this evidence, CCM may be considered in patients with AdvHF who are not candidates for heart transplant or LVAD (destination therapy) or as a bridge therapy to these treatments.

7. Percutaneous valve repair

Secondary (functional) mitral and tricuspid regurgitation are common in patients with AdvHF, and contribute negatively to symptoms and prognosis [76,77]. For this reason, new devices for transcatheter therapy of mitral and tricuspid regurgitation have been studied, and are now valid therapeutic options for selected patients with AdvHF.

7.1 Percutaneous repair of mitral regurgitation

The MitraClip System (Abbott, Abbott Park, IL, USA), which provides transcatheter edge-to-edge repair of the mitral valve, is the most widely used device for the treatment of secondary mitral regurgitation in patients with HFrEF. To date, >90,000 patients with severe mitral insufficiency have been treated with the MitraClip system. This represents an important non-surgical treatment option for patients with secondary mitral regurgitation who are still symptomatic despite optimized drug therapy and CRT (if indicated) and who are at high surgical risk [78]. Two landmark randomized studies have compared the MitraClip with drug therapy for secondary mitral regurgitation: COAPT and MITRA-FR [79,80]. In the COAPT study, patients undergoing MitraClip implantation had, at a 2-year follow-up, a reduction in mortality, reduced rehospitalizations, and improved quality of life compared with patients on medical therapy alone. In the MITRA-FR study, on the other hand, no change in mortality, re-hospitalizations and quality of life at 1-year follow-up was observed between the two treatment arms. The differences in outcomes between these studies were most likely due to the fact that MITRA-FR included patients with more left ventricular dilation (left ventricular end-diastolic volume index 135 mL/m^2 in MITRA-FR vs. 101 mL/m^2 in COAPT) and less severe mitral regurgitation (higher prevalence of patients with effective regurgitant orifice area <30 mm^2 in MITRA-FR) than COAPT, which enrolled patients with more severe functional mitral insufficiency and less dilated ventricles [81].

The MitraBridge registry enrolled 119 patients with severe functional mitral regurgitation and AdvHF that had undergone Mitralclip implantation. At 1-year follow-up, 64% of patients remained free from adverse events [82]. Based on these data and according to the recent European Society of Cardiology guidelines on diagnosis and management of HF [83], we recommend MitraClip implantation in patients with AdvHF and severe secondary mitral regurgitation that meet the inclusion criteria of COAPT.

7.2 Transcatheter mitral annuloplasty

In view of the findings that all valves with significant chronic mitral regurgitation have a certain degree of annular dilatation, and that the restoration of the physiological configuration of the annulus will improve the coaptation of the leaflets [84], in recent years several devices have been tested for direct or indirect percutaneous annuloplasty. Since these devices are still in the "embryonic" phase of research, a detailed description of these novel devices is beyond the scope of this review. Table 3 provides a summary of the most commonly used devices currently available in clinical practice.

8. Percutaneous repair of tricuspid regurgitation

Over the last decade, an increased understanding of the pathophysiology of tricuspid regurgitation and its detrimental effects, has led to the development of new devices for the percutaneous treatment of the tricuspid valve. To date, several devices have been approved for the treatment of functional tricuspid insufficiency. The data from the TriValve registry (which collects data on different devices) showed a procedural success rate of 72.8%, irrespective of the devices used [85]. A recent case-control study demonstrated that percutaneous treatment of tricuspid insufficiency at 1-year follow-up, resulted in improved survival (mortality 23.3% vs. 36.3%, $p < 0.001$) reduced hospitalizations for HF (26.3% vs. 47.3%, $p < 0.0001$) and better quality of compared with medical treatment alone [86]. Despite these promising results, the role of tricuspid valve repair in the management of patients with AdvHF is still not fully understood, and for this reason we recommend that the decision on whether to repair the tricuspid valve percutaneously must be "tailored" for each patient after careful evaluation by the heart team.

9. Surgery

The surgical treatment of end-stage HF has evolved significantly over the last several years [87]. Surgical options must be considered for AdvHF patients with severe symptoms and poor quality of life despite optimal medical and electrical device therapies [88]. Long-term surgical strategies for patients with AdvHF include LVAD and heart transplantation [89]. A detailed description of short-term temporary circulatory support systems that are sometimes used as a bridge to transplantation or LVAD in patients with cardiogenic shock, is beyond the scope of this review. However, in Table 4, we briefly describe the most commonly used devices for short-term circulatory support.

9.1 LVAD

LVAD therapy has evolved rapidly in recent years; and the latest generation of devices have improved durability, reduced surgical and thromboembolic complications, and

Table 5. Summarizes the principal indications and contraindications for LVAD implantation.

Indications	Contraindications
LVEF <25% and unable to exercise for HF, or if able to perform cardiopulmonary exercise testing, with peak VO_2 <12 mL/kg/min and/or <50% predicted value	Irreversible hepatic and/or renal disease
Three or more HF hospitalizations in previous 12 months without an obvious precipitating cause	Irreversible neurological disease
Dependence on IV inotropic therapy or temporary MCS	Severe right ventricular dysfunction and/or severe TR
Progressive end-organ dysfunction (worsening renal and/or hepatic function, type II pulmonary hypertension, cardiac cachexia) due to reduced perfusion and not to inadequately low ventricular filling pressure (PCWP $\geq$20 mmHg and SBP $\leq$90 mmHg or cardiac index $\leq$2 L/min/m^2)	Severe psychosocial limitation

Abbreviations: LVEF, Left Ventricular Ejection Fraction; HF, Heart Failure; MCS, Mechanical Circulatory Support; PCWP, Pulmonary Capillary Wedge Pressure; SBP, Systolic Blood Pressure; TR, Tricuspid Regurgitation.

Table 6. Indications and contraindications for heart transplants.

Indications	Contraindications
VO_2 $\leq$12 mL/kg/min in maximal cardiopulmonary exercise test in patients using b-blockers	Fixed pulmonary hypertension (PVR >5 Wood units)
VO_2 $\leq$14 mL/kg/min in maximal cardiopulmonary exercise test in patients not using b-blockers	Severe cerebrovascular diseases
VO_2 <50% predicted in maximal cardiopulmonary exercise test in young patients (<50 years) and women	Severe peripheral vascular diseases
VE/VCO_2 >35 in submaximal test	Severe liver or renal failure
Chronic coronary syndrome with refractory angina and with no possibility of revascularization	Severe pulmonary disease
Persistent and refractory ventricular arrhythmia	Severe psychiatric disease, chemical dependence, and poor compliance with treatment

improved patient survival [90]. Mechanical support with an LVAD can be used to maintain end organ perfusion in patients with AdvHF until they can receive a heart transplant (bridge to transplant) or as long-term support (destination therapy) if the patients are not eligible for a transplantation [91].

In Table 5 are summarized the main indications and contraindications to LVAD implant.

HeartMate 3 (Abbott, Abbott Park, IL, USA) is the most recent LVAD with approval from the US Food and Drug Administration for a bridge to transplant or destination therapy. This device has a magnetically levitated centrifugal pump that reduces blood stasis and improves hemocompatibility [92]. The HeartMate 3 was compared to the axial-flow HeartMate 2 in the MOMENTUM 3 trial. The HeartMate 3 was shown to be noninferior to the HeartMate 2 in terms of survival and reduction in hospitalizations, with a significantly lower need for device replacement due to malfunction of the device (relative risk 0.84; 95% CI 0.78–0.91; $p < 0.001$) [93]. Also, stroke, major bleeding, and gastrointestinal hemorrhage were decreased in the centrifugal flow–pump group compared to the axial flow–pump group. Based on these results, HeartMate 3 is now the device of choice for destination therapy and bridge therapy in patients with AdvHF, INTERMACS class 2–4, and preserved right ventricular function.

9.2 Heart transplantation

Heart transplantation is the gold-standard therapy for selected patients with AdvHF (Table 6). It results in significant improvements in survival, quality of life, and functional status compared with conventional treatments [94]. Improved selection of transplant candidates and improved posttransplant management of organ rejection have resulted in significant improvements in 1-year survival (>90%) and long-term survival, which now averages 12.2 years [95].

The UNOS (United Network of Organ Sharing in the United States) recently changed its organ-allocation policy to decrease waiting-list mortality and achieve equitable organ distribution [96]. The most critical changes in the new allocation system include higher priority for patients with temporary mechanical circulatory support over those inpatients awaiting transplantation on inotropic support alone, and prioritization for outpatients with restrictive or hypertrophic cardiomyopathy or congenital heart disease over those with dilated cardiomyopathy. Despite

heart transplants being the gold standard for AdvHF, organ scarcity limits the annual number of transplantations performed globally; therefore, a long-term circulatory support system will continue to be an important therapeutic alternative to heart transplantation.

10. Translational research and future direction

Current research focusing on myocardial recovery is desperately needed, since biochemical pathways capable of reversing, if not preventing, AdvHF would fundamentally change our approach to care.

Heart regeneration also has great potential to offer innovative therapy to treat patients with AdvHF [97]. Currently, there are several strategies for heart regeneration. Somatic stem cell transplantation has been shown in experimental models to be safe and to improve (albeit modestly) left ventricular function after myocardial infarction; primarily through paracrine mechanisms [98]. Alternatively, transplantation of induced pluripotent stem cells into the hearts of patients with AdvHF could lead (through production of new myocardiocytes) to improved myocardial performance [99].

More recently, direct cardiac reprogramming has emerged as a novel technology to regenerate damaged myocardium by directly converting endogenous cardiac fibroblasts into induced cardiomyocyte-like cells to restore cardiac function [100].

Other unmet needs of patients with AdvHF that will need to be addressed by upcoming research include better prediction of right ventricular dysfunction post LVAD implantation, improvement in ex situ perfusion techniques in order to increase the donor pool, as well as personalized approaches to immunosuppression to maximize graft durability and minimize infectious risk [101].

11. Conclusions

AdvHF is a clinical syndrome which is challenging to manage. Heart transplantation represents the optimal therapeutic strategy for these patients, but organ scarcity makes LVAD implantation another necessary option. In the coming years, significant efforts must be made to develop adequate clinical scoring systems to identify patients with AdvHF who need advanced surgical therapy. However, the need for resource optimization makes the role of the AdvHF team critical in appropriate patient selection for both heart transplantation and long-term LVAD therapy. Further clinical trials are needed to clarify the role of drug therapy, percutaneous valvular interventions, and cardiac implantable electronic device therapy in patients with AdvHF.

Author contributions

DM and AP writing the original draft, MK and GP reviewer and editing the original draft.

Ethics approval and consent to participate

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Conflict of interest

The authors declare no conflict of interest.

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