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Advanced heart failure: non-pharmacological approach

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Abstract
Patients with advanced heart failure have poor prognosis despite traditional pharmacological therapies. The early identification of these subjects would allow them to be addressed on time in dedicated centers to select patients eligible for heart transplantation or ventricular assistance. In this article we will report the current management of these patients based on latest international guidelines, underlining some critical aspects, with reference to future perspectives.

Keywords Chronic heart failure · Advanced heart failure · Heart transplantation

Introduction

Heart failure (HF) is the main cause of hospitalization and a major cause of disability in patients over 65 years of age, affecting at least 10 millions of patients in Europe. HF patients present a very poor prognosis, with a 5-year mortality of more than 50% [1]. Over the last decades, population aging and availability of more effective treatments have determined an increase in the number of patients suffering from advanced HF. Physicians with interest in HF should be trained in the management of such patients, requiring particular skills, tests, and procedures [2].

In this review, we summarize principal options in non-pharmacological treatment of advanced HF, from cardiac resynchronization therapy (CRT) to ablation of atrial fibrillation (AF) or ventricular tachycardias, from ventricular assist device (VAD) to heart transplantation (HT), and from

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ultrafiltration to transcatheter aortic valve implantation (TAVI) and mitral valve repair.

Definition of advanced heart failure

The "Heart Failure Association" of the European Society of Cardiology (ESC) defines advanced HF as a chronic condition characterized by severe and persistent symptoms (NYHA class III-IV) despite optimal guideline-directed treatment [3]; severe cardiac dysfunction defined by a reduced left ventricular ejection fraction (LVEF) ≤ 30%, isolated RV failure (e.g., arrhythmogenic right ventricular cardiomyopathy) 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 [4]; 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; and 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. The updated definition of advanced HF uses the most recent ESC HF guidelines. Using the ESC criteria for cardiac dysfunction gives the same importance to all patients with HF, independent of LVEF. In addition, now acute events leading to one or more unplanned visits or hospitalizations within 12 months are the hallmark of advanced HF, independent of treatment, with emphasis placed on the instability of the clinical course and resource utilization. Malignant arrhythmias have been added as a major cause of acute events.

"Advanced," "refractory," and "end-stage" HF can be considered interchangeable terms, all reflecting patients who should be evaluated for advanced HF therapies [3]. Advanced HF is characterized by symptoms limiting daily life such as anorexia, dyspnea, fatigue, pain, and depression [5]. The psycho-physical deterioration of the patient is also caused by ineffective continuous medical interventions and consequent anxiety for HF symptoms. A pattern of clinical characteristics may suggest which patients are worsening despite appropriate therapy **(**Table 1**).**

Table 1 Clinical features of worsening HF in HF patients despite appropriate therapy

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
6-min walk distance < 300 m
≥ 2 HF admissions in the last 12 months
O_2 unscheduled visits (e.g., ED or clinic) in 12 months
Worsening right heart failure 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 (persistent dyspnea during dressing or washing, which requires rest)
Systolic arterial pressure often < 90 mmHg
Increased 1-year mortality (e.g., 20%–25%) predicted by HF survival models (e.g., SHFM, HFSS)
Progressive renal or hepatic end-organ dysfunction
Persistent hyponatremia (serum sodium < 134 mEq/L)
Recurrent refractory ventricular tachyarrhythmias, frequent ICD shocks
Cardiac cachexia
Inability to perform ADL

Management of advanced heart failure

Advanced HF is usually characterized by a very aggressive evolution; so, patients with advanced HF should be followed by multidisciplinary teams of experts, including professionals other than cardiologists. An "advanced HF team" integrating hospital assistance, specialist outpatient assistance, and the general practitioner assistance is required. Contribution of other specialists, health and social workers, promotion of continuous training of all the professionals involved in the network, according to the evolution of knowledge, follow-up modalities and treatment options would be extremely useful for such patients [6].

Nevertheless, the prognosis of advanced HF remains poor, with higher mortality rates; early diagnosis may allow patients referral to specialized centers for tailored therapies or "extreme" solutions such as transplantation and LVAD.

Echocardiogram is usually not sufficient to diagnose advanced HF and right heart catheterization; the gold standard for the diagnosis of cardiac filling pressures is often required. Hemodynamic measurements at rest, in particular the pulmonary capillary wedging pressure, are closely related to the prognosis. However, catheterization is an expensive, invasive method with a consequent risk of complications [7]. Among the non-invasive methods for an early diagnosis of advanced HF, the cardiopulmonary test could play an important role; lower $PETCO_2$ levels are non-invasive independent predictors of LVAD implantation [8].

Non-pharmacological treatment of advanced HF

Cardiac resynchronization therapy

CRT is a clinically proven treatment which targets ventricular dyssynchrony, a condition present in a large percentage of

highly symptomatic HF patients [9]. CRT acts using artificial pacing, adding a LV lead to a standard right ventricular one in order to electrically stimulate muscle contraction of both chambers, usually placing the additional lead through the coronary sinus in contact with the lateral wall of the LV [10]. LV only pacing timed with native right ventricular activation is also reported [11,12]. CRT offers benefits both in the short-term through hemodynamic improvements and in the long-term via reverse remodeling of altered heart structures [9]. CRT biventricular pacing is usually associated with defibrillation implantation (CRT-D) [13].

Presently, divergent recommendations exist for CRT between main international guidelines, in particular about QRS morphology and duration but also with regard to atrial fibrillation (AF) and device choice (CRT-P or CRT-D). The comparison of recommendations for CRT is summarized in Table 2 [14]. The indication to CRT in patient with permanent AF and adequate rate control or atrioventricular nodal ablation is encouraged by recent observational studies [15]. Last ESC Guidelines on cardiac pacing and CRT and ACCF/AHA/HRS Guidelines on HF both propose to carefully evaluate patient risk profile before choosing between CRT-P and CRT-D [9,16,17]. CRT is effective in reducing hospitalization, reverse remodeling and mortality when patients are properly selected; proper patient selection for CRT still remains a matter of investigation.

CRT technology is continuously evolving with particular emphasis on improving lead design and delivery of resynchronization therapy, in order to minimize non-responder rates [18]. Recent studies stressed the importance of reducing the burden of AF and the number of (in) appropriate interventions. In this context, AF or even atrioventricular node ablation should also be considered [18,19]. Shock reducing strategies in patients with CRT-D consisting of ablation, adequate medical therapy, and proper device programming are associated with a significant lower risk of death as shown by MADIT-RIT and ADVANCE III studies [20,21].

Finally, CRT non-responder patients still represent a major issue despite modern technological advancement; in this respect both re-evaluation of selection criteria and use of new imaging techniques for pacing site choice should be considered [13].

The role of percutaneous treatment of secondary mitral regurgitation in patients with heart failure

Secondary mitral regurgitation (MR) is a common finding in patients with HF and LV dilatation. An appropriate medical therapy, based on current guidelines, plus CRT when indicated, may provide an improvement in symptoms, LV function, and in some patients, in the severity of MR [22].

On the other hand, surgical mitral valve repair or replacement does not seem to decrease the rate of hospitalization or death associated with secondary MR, and may be burdened by a considerable risk of complications [23]. Therefore, the majority of these patients are treated conservatively [24].

Treatment of secondary MR may be achieved with a percutaneous approach, approximating the anterior and posterior mitral leaflets to create a double-orifice valve. This technique, performed with the MitraClip device (Abbott), may result in a reduction of severity of MR.

Prospective registry studies suggest that percutaneous edge-to-edge mitral valve repair may produce a significant

Table 2 CRT—comparison of recommendations

Guidelines		ESC HFA (2016)	ESC EHRA (2013)	ACC/AHA/HRS (2013)	CCS (2017)	Australian Guidelines (2011)	NICE (2014)
QRS ≥ 150 ms with LBBB	NYHA III/IV	IA	IA	IA	I High	A	CRT-P or CRT-D
	NYHA II	IA	IA	IB	I High		CRT-D
QRS ≥ 150 ms without LBBB	NYHA III/IV	IIaB	IIaB	IIaA	IIb Low	A	CRT-P or CRT-D
	NYHA II	IIaB	IIaB	IIbB	IIb Low		CRT-D
QRS 130–149 with LBBB	NYHA III/IV	IB	IB	IIaB	I High	A	CRT-P or CRT-D
	NYHA II	IB	IB	IIaB	I High		CRT-D
QRS 130–149 without LBBB	NYHA III/IV	IIbB	IIbB	IIbB		A	CRT-P
	NYHA II	IIbB	IIbB	IIIB			
QRS 120–129 with LBBB	NYHA III/IV	IIIA	IB	IIaB	III Moderate	A	CRT-P or CRT-D
	NYHA II	IIIA	IB	IIaB	III Moderate		CRT-D
QRS 120–129 without LBBB	NYHA III/IV	IIIA	IIbB	IIbB	III Moderate	A	CRT-P
	NYHA II	IIIA	IIbB	IIIB	III Moderate		
AF and HF		IIaB	IIaB	IIaB	IIb Low		
Expected high % of ventricular pacing with reduced LVEF and symptomatic HF		IA	IIaB	IIaC	IIb Moderate		

reduction in symptoms and an improvement in functional capacity and quality of life in patients with secondary MR [25], but its role in advanced HF remains controversial.

Recently, the results of two prospective randomized studies analyzing the role of percutaneous edge-to-edge repair in addition to OMT compared to OMT alone, published with apparently contradictory results (the Mitra-FR study [26]) did not show significant difference between patients who underwent percutaneous mitral-valve repair in addition to OMT and those with OMT alone; instead, the COAPT Study [27] showed a lower rate of hospitalization for HF and lower all-cause mortality within 24 months of follow-up in patients in whom Mitraclip procedure was performed in addition to OMT when compared to OMT alone.

These apparently contradictory results may be explained by the differences in the patient' populations between the two studies; patients in the COAPT Study [27] had a higher degree of MR compared to the patients in the Mitra-FR study and a quite smaller LV. Furthermore, in the MITRA-FR trial there was a considerable variability of the medical therapy during the study time due to the real-world clinical practice, whereas in the COAPT trial, this was minimal. Finally, in the COAPT study there was a low rate of device-related complication plus an immediate achievement of MR $\leq$2+ in 95% of patients, with MR $\geq$3+ in only 0.9% of patients at 2-year follow-up.

In patients with advanced HF, with not extreme LV dilatation and secondary severe MR, percutaneous edge-to-edge repair, in addition to OMT, is a safe procedure that significantly reduces mortality, and more importantly, decreases hospitalization and improves quality of life. On the other hand, patients with a more severe LV dilatation do not seem to benefit from a percutaneous edge-to-edge procedure. A correct timing in the treatment of such patients is therefore crucial. A firmly adhesion to an OMT is also essential.

Transcatheter aortic valve implantation

Patients with aortic stenosis (AS) and concomitant HFrEF may be at risk for adverse effects from general anesthesia utilized in surgical aortic valve replacement (SAVR). Instead, TAVI has emerged as a gold standard therapeutic options for patients with symptomatic severe AS who are ineligible for SAVR or at high or intermediate operative risk. Few data are available on patients undergoing TAVI aged less than 75 years old or for surgical low-risk patients, where SAVR remains the reference method.

Available data from randomized controlled trials (RCT) and large registries in patients at increased surgical risk show that TAVI is superior in terms of mortality to medical therapy in extreme-risk patients [28], non-inferior or superior to surgery in high-risk patients and non-inferior to surgery in intermediate-risk patients [29–33]. The final decision between SAVR and TAVI (including the choice of access route) should be made by the Heart Team after careful individual evaluation [34].

Ablation of atrial fibrillation

About one third of HF patients develop AF; at the same time AF enhances by four to six times the risk of HF [35]. The prevalence of AF in HF increases according to the NYHA class [36–38].

AF with rapid ventricular response can induce LV systolic dysfunction (i.e., tachycardia-induced cardiomyopathy). New-onset AF in patients with HF is a precipitating factor of cardiac decompensation and was associated with increased risks of cardiovascular death, HF hospitalization, and stroke [39–42]. Definitive recommendations on the use of catheter ablation (CA) for AF in patients also suffering from HF are not available. Compared to medical therapy, patients treated with CA show significant improvement of LVEF, quality of life, and functional capacity, BNP levels and MLWHF scores, HF hospital readmissions, and death from any cause [43]. Most of them maintain sinus rhythm at 1 year with a single procedure [44]. CA in patients with LV systolic dysfunction is associated with significantly lower HF hospitalization rates, reduces all-cause mortality, increases 6-min walking test, improved LVEF, and peak oxygen consumption (VO_2) [45], without rising risks of serious adverse events [46]. Efficacy rates are lower among patients with persistent AF and long-standing persistent AF because the degree of atrial myopathy, scar burden, and co-morbidities influence outcomes. Pulmonary vein isolation (PVI) is the standard during all AF ablation procedures. Non-PV triggers are target for patients with persistent or long-standing persistent AF while PVI alone works better in patients with paroxysmal AF. Posterior wall isolation might be considered for initial or repeat ablation of persistent or long-standing persistent AF. Previous study showed that PVI was superior to AV node ablation and biventricular pacing [47,48] and showed better outcomes than antiarrhythmic drugs in patients with an ICD or CRT [49].

Ablation causes an improvement in LGE-based irreversible fibrosis [50–52] and improvements in ventricular and atrial chamber dimensions [53]. Early intervention with CA reduces interstitial fibrosis but also blocks the progression to scar and so it might minimize irreversible ventricular remodeling [54]. Recovery of LV function may explain the better outcomes with ablation in this population [55–57].

In the CASTLE-AF (Catheter Ablation Versus Standard Conventional Treatment in Patients with LV Dysfunction and Atrial Fibrillation) trial, CA appears superior in preserving sinus rhythm and improving LVEF in patients with LV dysfunction and AF [58]. The CABANA study (Catheter Ablation vs Anti-arrhythmic Drug Therapy for Atrial Fibrillation) showed a reduced mortality and cardiovascular hospitalization without a significant difference in primary

composite endpoint (death, disabling stroke, serious bleeding, and cardiac arrest) in the ablation group [59]. So, CA may be first-line therapy for the treatment of AF in patients with HFrEF regardless of AF type [60].

Ablation of ventricular tachyarrhythmias

Ventricular tachyarrhythmias (VTs) are common in advanced HF especially in patients supported with a LVAD [61]. VAs increased mortality from HF [62]. Antiarrhythmic drugs are not highly effective and poorly tolerated in these patients [63]. Ablation is recommended in patients with sustained monomorphic VT refractory to drugs and may be considered as first-line therapy in ischemic patients with ICD [64]. It can be acutely feasible to treat incessant VT and VT storms [65] because of high risk of adverse outcomes and ineffectiveness of medical therapy. Ablation is effective in preventing recurrence of VT in HF patients [66–68] but not reduce mortality [69,70].

Periprocedural acute HF can complicate ablation and is associated with a significant mortality risk. Some predictors of AHF are identified and high-risk patients can benefit from the use of mechanical circulatory support devices [71–73]. ECMO provides the best hemodynamic profile [74]. Prognosis for prophylactic use of ECMO is better than for rescue. Devices can be removed at the end of the procedure but some patients may require more prolonged periods of support. Mortality is highest in the ischemic cardiomyopathy [75]. The ablation goal are VT termination, ablation of diastolic or fragmented signals, and non-inducibility [76,77]. Sometimes a second ablation should be necessary because progressive remodeling generate additional substrates for re-entrant VTs [78].

Extracorporeal ultrafiltration in fluid overload management

Renal dysfunction is one of the most important comorbidities in HF. Worsening HF or acute decompensated HF can induce and/or accelerate renal injury. The first pharmacological option recommended by current ESC guidelines [4] for HF with fluid overload is optimization of diuretic therapy to increase water and sodium elimination. Extracorporeal ultrafiltration (UF) is suggested only when fluid overload persists even with the use of the highest-dose intravenous loop diuretics or the combination of different diuretic agents. This condition is defined as "diuretic resistance." UF resembles glomerular filtration and produces a fluid removal with minimal solute clearance and depurative effect. The process of UF consists of the production of plasma water from whole blood across a semipermeable membrane (pore sizes in the range of 0.1 to 0.001 μm) due to a transmembrane pressure gradient. A *Y*-shaped double-lumen catheter, a peristaltic pump, and a filter inserted in a veno-venous extracorporeal circuit are used. The pump determines a negative pressure, thus allowing blood circulation in the circuit from a vein to the filter, and then back to the patient. During the treatment, the progressive removal of plasma water will correspond to an equivalent replacement by fluids coming from the interstitial space, which in the HF is usually expanded. This happens thanks to the increased oncotic pressure secondary to the concentration of plasma proteins. The shift of plasma water from extravascular compartment (specifically the interstitial space) to the intravascular circulation is named vascular refilling rate (VRR), which could be estimated according the weight (VRR: 7–10 mL/kg/h) [79].

The optimal rate and duration of UF must be individualized; clinical experience teaches that extracorporeal fluid removal is better tolerated when conducted with low UF rates over prolonged periods of time [80,81]. Patients treated with UF had a more pronounced reduction in signs and symptoms of HF, and a significant decrease of NT-proBNP levels. A removal of liquids with adjustable rates and volumes maintains hemodynamic stability with no effect on serum electrolytes. UF causes a reduction of the filling pressures in the right and LV, of the circulating volumes, and of the pressures of the structures surrounding the heart. This allows the recovery of diuresis. The use of UF can rapidly improve symptoms, shorten of length of stay, and reduce numbers of re-hospitalizations [82–84].

On the other side, UF is an invasive procedure with several possible complications (hemolysis, coagulation of the circulation and reaction to the filter, hemorrhages and thrombocytopenia, pneumothorax and the risk of artery puncture, and finally, infections and occlusion of the catheter). All of these complications could be limited by an adequate clinical setting, and by cooperation between cardiologist and nephrologist with high experience in extracorporeal treatment management.

Ventricular assistance device

Although the number of HF patients has increased over the past 2 decades, the number of HT has remained relatively constant at around 3500–4000 per year due to the lack of donor organs [85]. This condition has increased the use of MCS: innovative technological advancements, especially the advent of smaller, durable continuous flow pumps, have led to the production of VAD that play an increasingly important role in the end-stage HF therapy.

The REMATCH trial first showed improved 1-year survival in inotrope-dependent, transplant-ineligible patients with advanced HF treated with an LVAD, but 2-year survival was not statistically different [86]. The currently systems in use for adults are second- and third-generation systems, which are significantly smaller and lighter than their predecessors from the first generation, and they have shown significant superiority over pulsatile first-generation devices.

Recently, the majority of patients treated with an implantable LVAD received a CF device, either a centrifugal pump

Table 3 Different uses for LVAD

Bridge to decision (BTD)–bridge to Bridge (BTB)	Use of short-term MCS (e.g., ECLS or ECMO) in patients with cardiogenic shock until hemodynamics and end-organ perfusion are stabilized, contra-indications for long-term MCS are excluded (brain damage after resuscitation), and additional therapeutic options including long-term VAD therapy or heart transplant can be evaluated
Bridge to candidacy (BTC)	Use of MCS (usually LVAD) to improve end-organ function in order to make an ineligible patient eligible for heart transplantation.
Bridge to transplantation (BTT)	Use of MCS (LVAD or BiVAD) to keep patient alive who is otherwise at high risk of death before transplantation until a donor organ becomes available.
Bridge to recovery (BTR)	Use of MCS (typically LVAD) to keep patient alive until cardiac function recovers sufficiently to remove MCS.
Destination therapy (DT)	Long-term use of MCS (LVAD) as an alternative to transplantation in patients with end-stage HF ineligible for transplantation or long-term waiting for heart transplantation.

such as the HeartWare HVAD (Medtronic, St. Paul, MN, USA) or an axial flow pump such as the HeartMate II (St. Jude Medical, Minneapolis, MN, USA). Nowadays, a new generation of magnetically levitated centrifugal pumps (HeartMate III, St. Jude Medical) is available in Europe. The pumps unload the heart by pumping blood from the LV to the ascending aorta. Contemporary LVADs are driven electrically via a percutaneous driveline connected to a small computer (controller) and external energy source, either batteries that are replaced every 4–12 h depending on the pump model or an AC power source. While the original pulsatile pumps had a limited life span, in most cases of < 2 years, the CF devices may last > 10 years [87].

Historically, LVADs have been used for short periods of time to ensure the survival of patients waiting for a donor organ ("bridge-to-transplant") [88]. Clinical studies have shown an improvement in survival in patients with advanced HF ineligible for transplantation treated with LVAD ("Destination Therapy") [89]. Another use for LVAD is "bridge-to-decision" for patients with relative contraindications or comorbidities for transplantation, reversible after a period of hemodynamic support **(**Table 3**).**

Whereas guidelines for HT listing exist, there are no universally accepted criteria for LVAD implantation [4]. Some commonly used indicators of illness severity include an LVEF ≤ 25%, frequent or prolonged HF hospitalizations, inability to tolerate standard HF treatments due to hypotension or renal insufficiency, and reduced maximal or submaximal exercise performance **(**Table 4**).** Most centers rely on the criteria used in clinical trials that candidate patients with hemodynamic imbalance including low cardiac index (< 2.2 L/min/m^2) and/or high left-sided filling pressures. HT listing criteria are important considerations in determining LVAD candidacy, but there are important distinctions between candidates for the two different treatments **(**Table 5**).** For example, pulmonary hypertension or recent cancer are important relative contraindications for transplantation but not for LVAD therapy, whereas patients with complex congenital heart disease or significant right ventricular (RV) failure [90] are less optimal LVAD candidates while they may have good outcomes with transplantation. Severe kidney failure is a contraindication for HT, but renal or liver function may improve after LVAD [91] as may pulmonary vascular resistance [92].

An important contribution to the selection for LVAD patients was the emergence of the INTERMACS classification [93] **(**Table 6**).** Outcomes in INTERMACS 3 (stable on inotropes) are better than in class 1–2: this is the optimal group for implantation of durable LVADs. The prospective ROADMAP study demonstrated superior survival with improvements in submaximal exercise performance in INTERMACS profile 4–7 patients treated with LVAD (HeartMate II) compared with patients treated with OMT [94].

The age is not a contraindication to implant of LVAD, as well as the ventricular arrhythmias or renal dysfunction but many elderly patients have multiorgan dysfunction, frailty, or other significant comorbidity that may compromise outcomes; the VTs may improve after LVAD implantation, but LVAD implantation may also be associated with increased tendency to VT. Patients with nephropathy and high-grade proteinuria or renal atrophy may be at very high risk, and few centers would accept patients on chronic dialysis because of the risk

Table 4 Main inclusion criteria for HeartMate II destination therapy (HM2-DT) trial

NYHA IIIb–IV symptoms for at least 45 of the last 60 days.
HF symptoms failed to respond to optimal medical management.
Peak VO_2 < 14 mL/kg/min or continued need for i.v. inotropic therapy owing to symptomatic hypotension, decreasing renal function, or worsening pulmonary congestion.
LVEF < 25%.
I.V. inotropic medications for ≥ 14 days.
Intra-aortic balloon pump support for ≥ 7 days.

Table 5 Distinctions between HT and LVAD candidates

	Cardiac transplant	LVAD
Body size	None	BSA < 1.2 m^2
Age	> 65–72	None (oldest reported > 88 years)
PVR (Woods units)	> 3	> 8
RV function	None	RVSWI < 250 mmHg × mL/m^2
Urgent situation	Yes	No
Comorbidities		
Malignancy	< 5 years disease-free	Chemotherapy non-completed
Renal	Creatinine > 2.5 mg/dL	Creatinine > 3 mg/dL
Pulmonary	Mild to moderate	Moderate to severe
Obesity	BMI > 30 kg/m^2	BMI > 45 kg/m^2
Intolerance to anticoagulation	No	Yes
Restrictive cardiomyopathy	No	Yes

of device infection and risk of poor outcome. Social network and even marital status are important factors in achieving good outcomes with LVAD therapy [95].

Common contraindications to implant of LVAD are, instead, active systemic bacterial or fungal infection in consideration of immunosuppressive therapy and untreated significant aortic regurgitation because it prevents pump flow from contributing to organ perfusion (Table 7).

Anticoagulation and antiplatelet therapies are important to prevent pump thrombosis. Both embolic ischemic events and bleeding events secondary to these therapies remain major complications of LVAD [96] and contribute to readmission and death [97].

HeartMate III group was associated with higher survival rates free of reoperation to remove or replace the device at 6-month post-implantation than HeartMate II group [98]. The HeartWare Ventricular Assist System for destination therapy of advanced HF was not inferior to HeartMate II with respect to primary end point of stroke-free survival or device removal due to malfunction [99].

Finally, the DuraHeart left ventricular assist system, the world's first approved magnetically levitated third-generation implantable centrifugal pump, demonstrated a significantly improved survival and reduced rates of adverse event and long-term reliability of devices compared to pulsatile LVADs [100,101].

Table 6 INTERMACS classification

INTERMACS level	NYHA class	Description	Device	1-year survival with LVAD therapy
I. Cardiogenic shock "Crash and burn"	IV	Hemodynamic instability in spite of increasing doses of catecholamines and/or mechanical circulatory support with critical hypoperfusion of target organs (severe cardiogenic shock).	ECLS, ECMO, percutaneous support devices	52.6 ± 5.6%
II. Progressive decline despite inotropic support "Sliding on inotropes"	IV	Intravenous inotropic support with acceptable blood pressure but rapid deterioration of renal function, nutritional state, or signs of congestion.	ECLS, ECMO, LVAD	63.1 ± 3.1%
III. Stable but inotrope dependent "Dependent stability"	IV	Hemodynamic stability with low or intermediate doses of inotropes, but necessary due to hypotension, worsening of symptoms, or progressive renal failure.	LVAD	78.4 ± 2.5%
IV. Resting symptoms "Frequent flyer"	IV ambulatory	Temporary cessation of inotropic treatment is possible, but patient presents with frequent symptom recurrences and typically with fluid overload	LVAD	78.7 ± 3.0%
V. Exertion intolerant "Housebound"	IV Ambulatory	Complete cessation of physical activity, stable at rest, but frequently with moderate fluid retention and some level of renal dysfunction	LVAD	93.0 ± 3.9%
VI. Exertion limited "Walking wounded"	III	Minor limitation on physical activity and absence of congestion while at rest. Easily fatigued by light activity.	LVAD/discuss LVAD as option	–
VII. "Placeholder"	III	Patients in NYHA Class III with no current or recent unstable fluid balance	Discuss LVAD as option	–

Table 7 Contraindication to LVAD

Active systemic bacterial or fungal infection
Untreated significant aortic regurgitation
Sources of compromised hemostasis (genetic bleeding disorders, severe hepatic insufficiency, etc.)
Nephropathy and high-grade proteinuria or renal atrophy
Substance abuse or alcoholism
Lack of social support
Right ventricular dysfunction
Elderly patients

Heart transplant

HT is the gold standard treatment of the end-stage HF, with severe symptoms, a poor prognosis, and no remaining alternative treatment options [102,103]. Patients that maintain functional classes III and IV, recurrent hospitalizations, present with poor prognostic markers, despite therapeutic optimization (with medications and surgery), should be considered for HT. Advances in immunosuppressive therapy have vastly improved the long-term survival of transplant recipients with a 1-, 3-, and 5-year post-transplant survival rate of 87.8%, 78.5%, and 71.7% in adults, respectively [104]. The greatest survival benefit is seen in those patients who are at highest risk of death from advanced HF [105].

Cardiopulmonary exercise testing helps refine candidate selection. Two parameters of the cardiopulmonary test are very useful, since they have a strong correlation with the prognosis of HF5: a peak oxygen consumption of < 14 mL/kg/min or < 12 mL/kg/min in patients on b-blockers at maximal exertion has been established as the cutoff point for HT [106]. If exercise is submaximal, a ventilation to carbon dioxide slope of > 35 also has prognostic value. A 6MWT < 300 m also indicates high risk. In patients with hemodynamic instability, HT may be performed emergently.

Table 8 Heart transplantation: indications and contraindications

Patients to consider	End-stage HF with severe symptoms, a poor prognosis, and no remaining alternative treatment options. Motivated, well informed, and emotionally stable. Capable of complying with the intensive treatment required post-operatively.
Contraindications	Absolute
	Systemic disease with life expectancy < 2 years: active neoplasm (if preexisting, evaluation with an oncology specialist is necessary to stratify the risk of recurrence and establish a time to wait after remission)
	Systemic disease with multiorgan involvement (systemic lupus erythematosus, amyloidosis, sarcoidosis)
	Severe chronic obstructive pulmonary disease (FEV1 < 1 L)
	Renal (e.g., creatinine clearance < 30 mL/min) or hepatic severe dysfunction, if associated renal or liver transplant is not performed
	Irreversible pulmonary hypertension
	Pulmonary artery systolic pressure > 50 mmHg
	Transpulmonary gradient > 12 mmHg
	Pulmonary vascular resistance > 3 Wood units despite treatment
	Relative
	Age > 70 years (carefully selected patients may be considered)
	Diabetes with end-organ damage (except non-proliferative retinopathy) or persistent poor glycemic control (HbA1c > 7.5%) despite treatment
	Active infection, except VAD infection. Patients with HIV, hepatitis, Chagas disease, and tuberculosis can be considered with strict management
	Severe peripheral arterial or cerebrovascular disease not suitable for treatment
	Other serious comorbidity with poor prognosis, such as neuromuscular diseases
	Obesity: BMI > 35 kg/m^2
	Cachexia: BMI < 18 kg/m^2
	Frailty: when three of five possible symptoms (including unintentional weight loss of > 5 kg within the past year, muscle loss, fatigue, slow walking speed, and low levels of physical activity) are present
	Current alcohol or drug abuse
	Insufficient social support
	Elevated panel-reactive antibody test defined as > 10%

The indications for and contraindications to HT are summarized in Table 8 [4]. Some contraindications are transient and treatable, such as untreated infections and neoplasms. Fixed pulmonary hypertension (especially with pulmonary vascular resistance > 3 Wood units) is a limiting factor, since it is associated with early post-operative right ventricle (RV) failure [107]. Pulmonary hypertension develops in response to a passive backward transmission of elevated filling pressures in the LV that with time causes vascular remodeling.

In patients listed for HT, the reversibility of pulmonary hypertension should be reassessed at 3- to 6-month intervals. LVAD can lower pulmonary hypertension and are used as a bridge to candidacy in patients with irreversible PH refractory to medical treatment [108].

Not less important, pretransplant immunological evaluation includes the determination of the panel of reactive antibodies against HLA (PRA), which can make the transplant unfeasible, if there is positivity against specific antigens of the donor [109].

Conclusions

The management of advanced HF patients need a specific HF unit, with an "Advanced HF team" (cardiologists, nephrologists, cardiac surgeons, electrophysiologists, physicians training for hemodynamic procedures and for cardiac rehabilitation), collective discussion of individual cases, and identification of the personalized management, integrating hospital assistance and promoting the continuous training of all the figures.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KK, Murabito JM, Vasan RS (2002) Long-term trends in the incidence of and survival with heart failure. N. Eng J Med. 347: 1397–1402
2. Dungen HD, Petroni R, Correale M, Coiro S, Monitillo F, Triggiani M, Leone M, Antohi EL, Ishihara S, Sarwar CMS, Sabbah HN, Memo M, Metra M, Butler J, Nodari S, Gheorghiade M (2018) A new educational program in heart failure drug development: the Brescia international master program. J Cardiovasc Med. 19:411–421
3. Crespo-Leiro MG, Metra M, Lund LH, Milicic D, Costanzo MR, Filippatos G, Gustafsson F, Tsui S, Barge-Caballero E, De Jonge N, Frigerio M, Hamdan R, Hasin T, Hülsmann M, Nalbantgil S, Potena L, Bauersachs J, Gkouziouta A, Ruhparwar A, Ristic AD, Straburzynska-Migaj E, McDonagh T, Seferovic P, Ruschitzka F (2018) Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 20:1505–1535
4. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, Van der Meer P (2016) 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 18:891–975
5. Lowey SE (2018) Palliative care in the management of patients with advanced heart failure. Adv Exp Med Biol. 1067:295–311
6. Aspromonte N, Gulizia MM, Di Lenarda A, Mortara A, Battistoni I, De Maria R, Gabriele M, Iacoviello M, Navazio A, Pini D, Di Tano G, Marini M, Ricci RP, Alunni G, Radini D, Metra M, Romeo F (2016) Documento di consenso ANMCO/SIC. La rete cardiologica per la cura del malato con scompenso cardiaco: organizzazione dell'assistenza ambulatoriale. G Ital Cardiol. 17: 570–593
7. Craig M, Pereira NL (2006) Right heart catheterization and risk stratification in advanced heart failure. Curr Heart Fail Rep. 3: 143–152
8. Seguchi O, Hisamatsu E, Nakano A, Nakajima S, Kuroda K, Watanabe T, Sato T, Sunami H, Yanase M, Hata H, Hamasaki T, Fujita T, Kobayashi J, Nakatani T, Kitakaze M, Fukushima N (2017) Low partial pressure of end-tidal carbon dioxide predicts left ventricular assist device implantation in patients with advanced chronic heart failure. Int J Cardiol. 230:40–46
9. Leeor M, Jaffe MD, Daniel P (2014) Morin. Cardiac resynchronization therapy: history, present status, and future directions. Ochsner J. 14:596–607
10. Turitto G, El-Sherif N (2007) Cardiac resynchronization therapy: a review of proarrhythmic and antiarrhythmic mechanisms. Pacing Clin Electrophysiol. 30:115–122
11. Burns KV, Gage RM, Curtin AE, Gorcsan J 3rd, Bank AJ (2017) Left ventricular-only pacing in heart failure patients with normal atrioventricular conduction improves global function and left ventricular regional mechanics compared with biventricular pacing: an adaptive cardiac resynchronization therapy sub-study. Eur J Heart Fail. 19:1335–1343
12. Urbanek B, Kaczmarek K, Klimczak A, Ruta J, Chudzik M, Piestrzeniewicz K, Ptaszynski P, Wranicz JK (2017) Potential benefit of optimizing atrioventricular & interventricular delays in patients with cardiac resynchronization therapy. Indian J Med Res. 146:71–77
13. Kosztin A, Boros AM, Geller L, Merkely B (2018) Cardiac resynchronization therapy: current benefits and pitfalls. Kardiol Pol. 76:1420–1425
14. Normand C, Linde C, Singh J, Dickstein K (2018) Indications for cardiac resynchronization therapy: a comparison of the major international guidelines. JACC Heart Fail. 6:308–316
15. Gasparini M, Auricchio A, Regoli F, Fantoni C, Kawabata M, Galimberti P, Pini D, Ceriotti C, Gronda E, Klersy C, Fratini S, Klein HH (2006) Four year efficacy of cardiac resynchronization therapy on exercise tolerance and disease progression: the importance of performing atrioventricular junction ablation in patients with atrial fibrillation. J Am Coll Cardiol 48:734–743
16. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, Di Carlo L, De Mets D, White BG, DeVries DW, Feldman AM (2004) Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 350:2140–2150
17. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson

MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchel JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines (2013) 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 62:e 147–239.

18. Auricchio A, Heggermont WA (2018) Technology advances to improve response to cardiac resynchronization therapy: what clinicians should know. Rev. Esp Cardiol. 71:477–484
19. Marrouche NF, Brachmann J, Committee C-AS (2009) Catheter ablation versus standard conventional treatment in patients with left ventricular dysfunction and atrial fibrillation (CASTLE-AF)—study design. Pacing Clin Electrophysiol. 32:987–994
20. Moss AJ, Schuger C, Beck CA, Brown MW, Cannom DS, Daubert JP, Estes NAM, Greenberg H, Hall WJ, Huang DT, Kautzner J, Klein H, McNitt S, Olshansky B, Shoda M, Wilber D, Zareba W (2012) Reduction in inappropriate therapy and mortality through ICD programming. N Engl J Med. 367:2275–2283
21. Kloppe A, Proclemer A, Arenal A, Lunati M, Martìnez Ferrer JB, Hersi A, Gulaj M, Wijffels MC, Santi E, Manotta L, Mangoni L, Gasparini M (2014) Efficacy of long detection interval implantable cardioverter-defibrillator settings in secondary prevention population: data from the Avoid Delivering Therapies for Nonsustained Arrhythmias in ICD Patients III (ADVANCE III) trial. Circulation. 130:308–314
22. Stone GW, Vahanian AS, Adams DH, Abraham WT, Borer JS, Bax JJ, Schofer J, Cutlip DE, Krucoff MW, Blackstone EH, Généreux P, Mack MJ, Siegel RJ, Grayburn PA, Enriquez-Sarano M, Lancellotti P, Filippatos G, Kappetein AP (2015) Clinical trial design principles and endpoint definitions for transcatheter mitral valve repair and replacement: Part 1: clinical trial design principles—a consensus document from the Mitral Valve Academic Research Consortium. J Am Coll Cardiol. 66:278–307
23. Asgar AW, Mack MJ, Stone GW (2015) Secondary mitral regurgitation in heart failure: pathophysiology, prognosis, and therapeutic considerations. J Am Coll Cardiol. 65:1231–1248
24. Goel SS, Bajaj N, Aggarwal B, Gupta S, Poddar KL, Ige M, Bdair H, Anabtawi A, Rahim S, Whitlow PL, Tuzcu EM, Griffin BP, Stewart WJ, Gillinov M, Blackstone EH, Smedira NG, Oliveira GH, Barzilai B, Menon V, Kapadia SR (2014) Prevalence and outcomes of unoperated patients with severe symptomatic mitral regurgitation and heart failure: comprehensive analysis to determine the potential role of MitraClip for this unmet need. J Am Coll Cardiol. 63:185–186
25. Maisano F, Franzen O, Baldus S, Schäfer U, Hausleiter J, Butter C, Ussia GP, Sievert H, Richardt G, Widder JD, Moccetti T, Schillinger W (2013) Percutaneous mitral valve interventions in the real world: early and 1-year results from the ACCESS-EU, a prospective, multicenter, nonrandomized post-approval study of the MitraClip therapy in Europe. J Am Coll Cardiol. 62:1052–1061
26. Obadia JF, Messika-Zeitoun D, Leurent G, Iung B, Bonnet G, Piriou N, Lefèvre T, Piot C, Rouleau F, Carrié D, Nejjari M, Ohlmann P, Leclercq F, Saint Etienne C, Teiger E, Leroux L, Karam N, Michel N, Gilard M, Donal E, Trochu JN, Cormier B, Armoiry X, Boutitie F, Maucort-Boulch D, Barnel C, Samson G, Guerin P, Vahanian A, Mewton N, MITRA-FR Investigators (2018) Percutaneous repair or medical treatment for secondary mitral regurgitation. N Engl J Med. 379:2297–2306
27. Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, Whisenant B, Grayburn PA, Rinaldi M, Kapadia SR, Rajagopal V, Sarembock IJ, Brieke A, Marx SO, Cohen DJ, Weissman NJ, Mack MJ, COAPT Investigators (2018) Transcatheter mitral-valve repair in patients with heart failure. N Engl J Med. 379:2307–2318
28. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S, PARTNER Trial Investigators (2010) Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med. 363:1597–1607
29. Deeb GM, Reardon MJ, Chetcuti S, Patel HJ, Grossman PM, Yakubov SJ, Kleiman NS, Coselli JS, Gleason TG, Lee JS, Hermiller JB Jr, Heiser J, Merhi W, Zorn GL 3rd, Tadros P, Robinson N, Petrossian G, Hughes GC, Harrison JK, Maini B, Mumtaz M, Conte J, Resar J, Aharonian V, Pfeffer T, Oh JK, Qiao H, Adams DH, Popma JJ, CoreValve US Clinical Investigators (2016) 3-year outcomes in high-risk patients who underwent surgical or transcatheter aortic valve replacement. J Am Coll Cardiol. 67:2565–2574
30. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ, PARTNER Trial Investigators (2011) Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med. 364:2187–2198
31. Mack MJ, Leon MB, Smith CR, Miller DC, Moses JW, Tuzcu EM, Webb JG, Douglas PS, Anderson WN, Blackstone EH, Kodali SK, Makkar RR, Fontana GP, Kapadia S, Bavaria J, Hahn RT, Thourani VH, Babaliaros V, Pichard A, Herrmann HC, Brown DL, Williams M, Akin J, Davidson MJ, Svensson LG, PARTNER 1 Trial Investigators (2015) 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomized controlled trial. Lancet 385:2477–2484
32. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, Gleason TG, Buchbinder M, Hermiller J Jr, Kleiman NS, Chetcuti S, Heiser J, Merhi W, Zorn G, Tadros P, Robinson N, Petrossian G, Hughes GC, Harrison JK, Conte J, Maini B, Mumtaz M, Chenoweth S, Oh JK, U.S., CoreValve Clinical Investigators (2014) Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med. 370:1790–1798
33. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, Thourani VH, Tuzcu EM, Miller DC, Herrmann HC, Doshi D, Cohen DJ, Pichard AD, Kapadia S, Dewey T, Babaliaros V, Szeto WY, Williams MR, Kereiakes D, Zajarias A, Greason KL, Whisenant BK, Hodson RW, Moses JW, Trento A, Brown DL, Fearon WF, Pibarot P, Hahn RT, Jaber WA, Anderson WN, Alu MC, Webb JG, PARTNER 2 Investigators (2016) Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. N Engl J Med 374:1609–1620
34. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Muñoz DR, Rosenhek R, Sjögren J, Mas PT, Vahanian A, Wendler TWO, Windecker S, Zamorano JL, ESC Scientific Document Group (2017) 2017 ESC/EACTS Guidelines for the management of valvular heart disease The Task Force for the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 38:2739–2791
35. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna W, Seward JB, Iwasaka T, Tsang TS (2006) Incidence and mortality risk of congestive heart failure in atrial fibrillation patients: a community-based study over two decades. Eur Heart J. 27:936–941
36. Tsang TS, Gersh BJ (2002) Atrial fibrillation: an old disease, a new epidemic. Am J Med. 113:432–435
37. Jons C, Jacobsen UG, Joergensen RM, Olsen NT, Dixen U, Johannessen A, Huikuri H, Messier M, McNitt S, Thomsen PE, Cardiac Arrhythmias and Risk Stratification after Acute

Myocardial Infarction (CARISMA) Study Group (2011) The incidence and prognostic significance of new-onset atrial fibrillation in patients with acute myocardial infarction and left ventricular systolic dysfunction: a CARISMA substudy. Heart Rhythm. 8: 342–348

38. Cleland JG, Swedberg K, Cohen-Solal A, Cosin-Aguilar J, Dietz R, Follath F, Gavazzi A, Hobbs R, Korewicki J, Madeira HC, Preda I, van Gilst WH, Widimsky J, Mareev V, Mason J, Freemantle N, Eastaugh J (2000) The Euro Heart Failure Survey of the EUROHEART survey programme. A survey on the quality of care among patients with heart failure in Europe. The Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The Medicines Evaluation Group Centre for Health Economics University of York. Eur J Heart Fail 2:123–132
39. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, D'Agostino RB, Murabito JM, Kannel WB, Benjamin EJ (2003) Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. Circulation. 107:2920–2925
40. Mogensen UM, Jhund PS, Abraham WT, Desai AS, Dickstein K, Packer M, Rouleau JL, Solomon SD, Swedberg K, Zile MR, Køber L, McMurray JJV, PARADIGM-HF and ATMOSPHERE Investigators and Committees (2017) Type of atrial fibrillation and outcomes in patients with heart failure and reduced ejection fraction. J Am Coll Cardiol 70:2490–2500
41. Arrigo M, Gayat E, Parenica J, Ishihara S, Zhang J, Choi DJ, Park JJ, Alhabib KF, Sato N, Miro O, Maggioni AP, Zhang Y, Spinar J, Cohen-Solal A, Iwashyna TJ, Mebazaa A, GREAT Network (2017) Precipitating factors and 90-day outcome of acute heart failure: a report from the intercontinental GREAT registry. Eur J Heart Fail. 19:201–208
42. McMurray JJ, Ezekowitz JA, Lewis BS, Gersh BJ, van Diepen S, Amerena J, Bartunek J, Commerford P, Oh BH, Harjola VP, Al-Khatib SM, Hanna M, Alexander JH, Lopes RD, Wojdyla DM, Wallentin L, Granger CB, ARISTOTLE Committees and Investigators (2013) Left ventricular systolic dysfunction, heart failure, and the risk of stroke and systemic embolism in patients with atrial fibrillation: insights from the ARISTOTLE trial. Circ Heart Fail. 6:451–460
43. Smer A, Salih M, Darrat YH, Saadi A, Guddeti R, Mahfood Haddad T, Kabach A, Ayan M, Saurav A, Abuissa H, Elayi CS (2018) Meta-analysis of randomized controlled trials on atrial fibrillation ablation in patients with heart failure with reduced ejection fraction. Clin Cardiol. 41:1430–1438
44. Jones DG, Haldar SK, Hussain W, Sharma R, Francis DP, Rahman-Haley SL, McDonagh TA, Underwood SR, Markides V, Wong T (2013) A randomized trial to assess catheter ablation versus rate control in the management of persistent atrial fibrillation in heart failure. J Am Coll Cardiol. 61:1894–1903
45. Hunter RJ, Berriman TJ, Diab I, Kamdar R, Richmond L, Baker V, Goromonzi F, Sawhney V, Duncan E, Page SP, Ullah W, Unsworth B, Mayet J, Dhinoja M, Earley MJ, Sporton S, Schilling RJ (2014) A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (the CAMTAF trial). Circ Arrhythm Electrophysiol. 7:31–38
46. Kheiri B, Osman M, Abdalla A, Haykal T, Ahmed S, Bachuwa G, Hassan M, Bhatt DL (2018) Catheter ablation of atrial fibrillation with heart failure: an updated meta-analysis of randomized trials. Int J Cardiol. 269:170–173
47. Preobrazhenskii DV (2009) What is the optimal catheter approach for atrial fibrillation in chronic heart failure? Is it rhythm control or rate control? Results of PABA-CHF study. Kardiologiia. 49:70–71
48. Khan MN, Jaïs P, Cummings J, Di Biase L, Sanders P, Martin DO, Kautzner J, Hao S, Themistoclakis S, Fanelli R, Potenza D, Massaro R, Wazni O, Schweikert R, Saliba W, Wang P, Al-Ahmad A, Beheiry S, Santarelli P, Starling RC, Dello Russo A, Pelargonio G, Brachmann J, Schibgilla V, Bonso A, Casella M, Raviele A, Haïssaguerre M, Natale A, PABA-CHF Investigators (2008) Pulmonary-vein isolation for atrial fibrillation in patients with heart failure. N Engl J Med. 359:1778–1785
49. Di Biase L, Mohanty P, Mohanty S, Santangeli P, Trivedi C, Lakkireddy D, Reddy M, Jais P, Themistoclakis S, Dello Russo A, Casella M, Pelargonio G, Narducci ML, Schweikert R, Neuzil P, Sanchez J, Horton R, Beheiry S, Hongo R, Hao S, Rossillo A, Forleo G, Tondo C, Burkhardt JD, Haissaguerre M, Natale A (2016) Ablation versus amiodarone for treatment of persistent atrial fibrillation in patients with congestive heart failure and an implanted device: results from the AATAC multicenter randomized trial. Circulation 133:1637–1644
50. Addison D, Farhad H, Shah RV, Mayrhofer T, Abbasi SA, John RM, Michaud GF, Jerosch-Herold M, Hoffmann U, Stevenson WG, Kwong RY, Neilan TG (2016) Effect of late gadolinium enhancement on the recovery of left ventricular systolic function after pulmonary vein isolation. J Am Heart Assoc. 5:e003570
51. Tzou WS (2018) Additional clarity provided through the lens of CAMERA-MRI: why patients with heart failure and atrial fibrillation may benefit from catheter ablation. JACC Clin Electrophysiol 4:1008–1010
52. aus dem Siepen F, Buss SJ, Messroghli D, Andre F, Lossnitzer D, Seitz S, Keller M, Schnabel PA, Giannitsis E, Korosoglou G, Katus HA, Steen H (2015) T1 mapping in dilated cardiomyopathy with cardiac magnetic resonance: quantification of diffuse myocardial fibrosis and comparison with endomyocardial biopsy. Eur Heart J Cardiovasc Imaging 16:210–216
53. Prabhu S, Taylor AJ, Costello BT, Kaye DM, McLellan AJA, Voskoboinik A, Sugumar H, Lockwood SM, Stokes MB, Pathik B, Nalliah CJ, Wong GR, Azzopardi SM, Gutman SJ, Lee G, Layland J, Mariani JA, Ling LH, Kalman JM, Kistler PM (2017) Catheter ablation versus medical rate control in atrial fibrillation and systolic dysfunction: the CAMERA-MRI Study. J Am Coll Cardiol. 70:1949–1961
54. Prabhu S, Costello BT, Taylor AJ, Gutman SJ, Voskoboinik A, McLellan AJA, Peck KY, Sugumar H, Iles L, Pathik B, Nalliah CJ, Wong GR, Azzopardi SM, Lee G, Mariani J, Kaye DM, Ling LH, Kalman JM, Kistler PM (2018) Regression of diffuse ventricular fibrosis following restoration of sinus rhythm with catheter ablation in patients with atrial fibrillation and systolic dysfunction: a substudy of the CAMERA MRI trial. JACC Clin Electrophysiol 4:999–1007
55. Prabhu S, Ling LH, Ullah W, Hunter RJ, Schilling RJ, McLellan AJ, Earley MJ, Sporton SC, Voskoboinik A, Blusztein D, Mariani JA, Lee G, Taylor AJ, Kalman JM, Kistler PM (2016) The impact of known heart disease on long-term outcomes of catheter ablation in patients with atrial fibrillation and left ventricular systolic dysfunction: a multicenter international study. J Cardiovasc Electrophysiol. 27:281–289
56. Anselmino M, Matta M, D'ascenzo F, Pappone C, Santinelli V, Bunch TJ, Neumann T, Schilling RJ, Hunter RJ, Noelker G, Fiala M, Frontera A, Thomas G, Katritsis D, Jais P, Weerasooriya R, Kalman JM, Gaita F (2015) Catheter ablation of atrial fibrillation in patients with diabetes mellitus: a systematic review and meta-analysis. Europace 17:1518–1525
57. Ullah W, Ling LH, Prabhu S, Lee G, Kistler P, Finlay MC, Earley MJ, Sporton S, Bashir Y, Betts TR, Rajappan K, Thomas G, Duncan E, Staniforth A, Mann I, Chow A, Lambiase P, Schilling RJ, Hunter RJ (2016) Catheter ablation of atrial fibrillation in patients with heart failure: impact of maintaining sinus rhythm on heart failure status and long-term rates of stroke and death. Europace. 18:679–686
58. Marrouche NF (2018) Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, Merkely B, Pokushalov E, Sanders P,

Proff J, Schunkert H, Christ H, Vogt J, Bänsch D; CASTLE-AF Investigators. Catheter ablation for atrial fibrillation with heart failure. N Engl J Med. 378:417–427
59. Packer DL, Mark DB, Robb RA, Monahan KH, Bahnson TD (2018) Moretz K, Poole JE, Mascette A, Rosenberg Y, Jeffries N, Al-Khalidi HR, Lee KL; CABANA Investigators. Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) Trial: study rationale and design. Am Heart J. 199:192–199
60. Baher A, Marrouche NF (2018) Treatment of atrial fibrillation in patients with co-existing heart failure and reduced ejection fraction: time to revisit the management guidelines? Arrhythm Electrophysiol Rev. 7:91–94
61. Pedrotty DM, Rame JE, Margulies KB (2013) Management of ventricular arrhythmias in patients with ventricular assist devices. Curr Opin Cardiol. 28:360–368
62. Tzou WS, Tung R, Frankel DS, Vaseghi M, Bunch TJ, Di Biase L, Tholakanahalli VN, Lakkireddy D, Dickfeld T, Saliaris A, Weiss JP, Mathuria N, Tedrow U, Afzal MR, Vergara P, Nagashima K, Patel M, Nakahara S, Vakil K, Burkhardt JD, Tseng CH, Natale A, Shivkumar K, Callans DJ, Stevenson WG, Della Bella P, Marchlinski FE, Sauer WH. Ventricular tachycardia ablation in severe heart failure: an international ventricular tachycardia ablation center collaboration analysis. Circ Arrhythm Electrophysiol, 2017;10(1).
63. Baher A, Valderrabano M (2013) Management of ventricular tachycardia in heart failure. Methodist Debakey Cardiovasc J. 9: 20–25
64. Pedersen CT, Kay GN, Kalman J, Borggrefe M, Della-Bella P, Dickfeld T, Dorian P, Huikuri H, Kim YH, Knight B, Marchlinski F, Ross D, Sacher F, Sapp J, Shivkumar K, Soejima K, Tada H, Alexander ME, Triedman JK, Yamada T, Kirchhof P, Lip GY, Kuck KH, Mont L, Haines D, Indik J, Dimarco J, Exner D, Iesaka Y, Savelieva I, EP-Europace, UK (2014) EHRA/HRS/APHRS expert consensus on ventricular arrhythmias. Heart Rhythm. 11:e166–e196
65. Carbucicchio C, Santamaria M, Trevisi N, Maccabelli G, Giraldi F, Fassini G, Riva S, Moltrasio M, Cireddu M, Veglia F, Della BP (2008) Catheter ablation for the treatment of electrical storm in patients with implantable cardioverter-defibrillators: short- and long-term outcomes in a prospective single-center study. Circulation. 117:462–469
66. Mallidi J, Nadkarni GN, Berger RD, Calkins H, Nazarian S (2011) Meta-analysis of catheter ablation as an adjunct to medical therapy for treatment of ventricular tachycardia in patients with structural heart disease. Heart Rhythm. 8:503–510
67. Ellenbogen KA, Kaszala K (2010) Ventricular tachycardia ablation: what have we learned from SMASH-VT. J Cardiovasc Electrophysiol. 21:804–805
68. Kuck KH, Schaumann A, Eckardt L, Willems S, Ventura R, Delacretaz E, Pitschner HF, Kautzner J, Schumacher B, Hansen PS, Vtach study group (2010) Catheter ablation of stable ventricular tachycardia before defibrillator implantation in patients with coronary heart disease (VTACH): a multicentre randomized controlled trial. Lancet 375:31–40
69. Santangeli P, Muser D, Maeda S, Filtz A, Zado ES, Frankel DS, Dixit S, Epstein AE, Callans DJ, Marchlinski FE (2016) Comparative effectiveness of antiarrhythmic drugs and catheter ablation for the prevention of recurrent ventricular tachycardia in patients with implantable cardioverter-defibrillators: a systematic review and meta-analysis of randomized controlled trials. Heart Rhythm. 13:1552–1559
70. Sapp JL, Wells GA, Parkash R, Stevenson WG, Blier L, Sarrazin JF, Thibault B, Rivard L, Gula L, Leong-Sit P, Essebag V, Nery PB, Tung SK, Raymond JM, Sterns LD, Veenhuyzen GD, Healey JS, Redfearn D, Roux JF, Tang AS (2016) Ventricular tachycardia ablation versus escalation of antiarrhythmic drugs. N Engl J Med. 375:111–121
71. Mathuria N, Wu G, Rojas-Delgado F, Shuraih M, Razavi M, Civitello A, Simpson L, Silva G, Wang S, Elayda M, Kantharia B, Singh S, Frazier OH, Cheng J (2017) Outcomes of pre-emptive and rescue use of percutaneous left ventricular assist device in patients with structural heart disease undergoing catheter ablation of ventricular tachycardia. J Interv Card Electrophysiol. 48:27–34
72. Aryana A, Gearoid O'Neill P, Gregory D, Scotti D, Bailey S, Brunton S, Chang M, d'Avila A (2014) Procedural and clinical outcomes after catheter ablation of unstable ventricular tachycardia supported by a percutaneous left ventricular assist device. Heart Rhythm. 11:1122–1130
73. Lu F, Eckman PM, Liao KK, Apostolidou I, John R, Chen T, Das GS, Francis GS, Lei H, Trohman RG, Benditt DG (2013) Catheter ablation of hemodynamically unstable ventricular tachycardia with mechanical circulatory support. Int J Cardiol. 168:3859–3865
74. Ostadal P, Mlcek M, Holy F, Horakova S, Kralovec S, Skoda J, Petru J, Kruger A, Hrachovina V, Svoboda T, Kittnar O, Reddy VY, Neuzil P (2012) Direct comparison of percutaneous circulatory support systems in specific hemodynamic conditions in a porcine model. Circ Arrhythm Electrophysiol. 5:1202–1206
75. Kumar S, Romero J, Mehta NK, Fujii A, Kapur S, Baldinger SH, Barbhaiya CR, Koplan BA, John RM, Epstein LM, Michaud GF, Tedrow UB, Stevenson WG (2016) Long-term outcomes after catheter ablation of ventricular tachycardia in patients with and without structural heart disease. Heart Rhythm. 13:1957–1963
76. Stevenson WG, Friedman PL, Ganz LI (1997) Radiofrequency catheter ablation of ventricular tachycardia late after myocardial infarction. J Cardiovasc Electrophysiol. 8:1309–1319
77. Stevenson WG, Sager P, Nademanee K, Hassan H, Middlekauff HR, Saxon LA, Wiener I (1992) Identifying sites for catheter ablation of ventricular tachycardia. Herz. 17:158–170
78. Frankel DS, Mountantonakis SE, Robinson MR, Zado ES, Callans DJ, Marchlinski FE (2011) Ventricular tachycardia ablation remains treatment of last resort in structural heart disease: argument for earlier intervention. J Cardiovasc Electrophysiol. 22:1123–1128
79. Schroeder KL, Sallustio JE, Ross EA (2004) Continuous hematocrit monitoring during intradialytic hypotension: precipitous decline in plasma refill rates. Nephrol Dial Transplant. 19:652–656
80. Schrier RW, Bansal S (2008) Pulmonary hypertension, right ventricular failure, and kidney: different from left ventricular failure? Clin J Am Soc Nephrol. 3:1232–1237
81. Costanzo MR, Ronco C, Abraham WT, Agostoni P, Barasch J, Fonarow GC, Gottlieb SS, Jaski BE, Kazory A, Levin AP, Levin HR, Marenzi G, Mullens W, Negoianu D, Redfield MM, Tang WHW, Testani JM, Voors AA (2017) Extracorporeal ultrafiltration for fluid overload in heart failure: current status and prospects for further research. J Am Coll Cardiol. 69:2428–2445
82. Costanzo MR, Saltzberg MT, Jessup M, Teerlink JR (2010) Sobotka PA; Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD) Investigators. Ultrafiltration is associated with fewer rehospitalizations than continuous diuretic infusion in patients with decompensated heart failure: results from UNLOAD. J Card Fail. 16:277–284
83. Giglioli C, Landi D, Cecchi E, Chiostri M, Gensini GF, Valente S, Ciaccheri M, Castelli G, Romano SM (2011) Effects of ULTRAfiltration vs. DIureticS on clinical, biohumoral and haemodynamic variables in patients with deCOmpensated heart failure: the ULTRADISCO study. Eur J Heart Fail. 13:337–346
84. Marenzi G, Muratori M, Cosentino ER, Rinaldi ER, Donghi V, Milazzo V, Ferramosca E, Borghi C, Santoro A, Agostoni P (2014) Continuous ultrafiltration for congestive heart failure: the CUORE trial. J Card Fail. 20:9–17

85. Toyoda Y, Guy TS, Kashem A (2013) Present status and future perspectives of heart transplantation. Circ J. 77:1097–1110
86. Rose EA, Gelijns AC, Moskowitz AJ, Heitjan DF, Stevenson LW, Dembitsky W, Long JW, Ascheim DD, Tierney AR, Levitan RG, Watson JT, Meier P, Ronan NS, Shapiro PA, Lazar RM, Miller LW, Gupta L, Frazier OH, DesvigneNickens P, Oz MC (2001) Poirier VL; 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. 345:1435–1443
87. Gustafsson F, Rogers JG (2017) Left ventricular assist device therapy in advanced heart failure: patient selection and outcomes. Eur J Heart Fail. 19:595–602
88. Miller LW, Pagani FD, Russell SD, John R, Boyle AJ, Aaronson KD, Conte JV, Naka Y, Mancini D, Delgado RM, Macgilliray TE, Farrar D, Frazier OH (2007) Use of a continuous-flow device in patients awaiting heart transplantation. N Engl J Med. 357:885–896
89. Rose EA, Gelijns AC, Moskowitz AJ, Heitjan DF, Stevenson LW, Dembitsky W, Long JW, Ascheim DD, Tierney AR, Levitan RG, Watson JT, Meier P, Ronan NS, Shapiro PA, Lazar RM, Miller LW, Gupta L, Frazier OH, Desvigne-Nickens P, Oz MC, Poirier VL (2001) Long-term use of a left ventricular assist device for end-stage heart failure. N Engl J Med. 345:1435–1443
90. Harjola VP, Mebazaa A, Celutkiene J, Bettex D, Bueno H, Chioncel O, Crespo-Leiro MG, Falk V, Filippatos G, Gibbs S, Leite-Moreira A, Lassus J, Masip J, Mueller C, Mullens W, Naeije R, Nordegraaf AV, Parissis J, Riley JP, Ristic A, Rosano G, Rudiger A, Ruschitzka F, Seferovic P, Sztrymf B, Vieillard-Baron A, Yilmaz MB, Konstantinides S (2016) Contemporary management of acute right ventricular failure: a statement from the Heart Failure Association and the Working Group on Pulmonary Circulation and Right Ventricular Function of the European Society of Cardiology. Eur J Heart Fail 18:226–241
91. Hasin T, Topilsky Y, Schirger JA, Li Z, Zhao Y, Boilson BA, Clavell AL, Rodeheffer RJ, Frantz RP, Edwards BS, Pereira NL, Joyce L, Daly R, Park SJ, Kushwaha SS (2012) Changes in renal function after implantation of continuous flow left ventricular assist devices. J Am Coll Cardiol. 59:26–36
92. Mikus E, Stepanenko A, Krabatsch T, Loforte A, Dandel M, Lehmkuhl HB, Hetzer R, Potapov EV (2011) Reversibility of fixed pulmonary hypertension in left ventricular assist device support recipients. Eur J Cardiothorac Surg. 40:971–977
93. Stevenson LW, Couper G (2007) On the fledgling field of mechanical circulatory support. J Am Coll Cardiol. 50:748–751
94. Estep JD, Starling RC, Horstmanshof DA, Milano CA, Selzman CH, Shah KB, Loebe M, Moazami N, Long JW, Stehlik J, Kasirajan V, Haas DC, O'Connell JB, Boyle AJ, Farrar DJ, Rogers JG (2015) Risk assessment and comparative effectiveness of left ventricular assist device and medical management in ambulatory heart failure patients: results from the ROADMAP study. J Am Coll Cardiol. 66:1747–1761
95. Wright GA, Rauf A, Stoker S, Alharethi R, Kfoury AG (2015) Marital status and survival in left ventricular assist device patient populations. J Heart Lung Transplant. 34:619–621
96. Correale M, Ieva R, Pappalardo F, Santoro F, De Bonis M, Di Biase M (2013) Gastrointestinal bleeding and coagulation disorders in a patient with left-ventricular assist device. J Cardiovasc Med. 14:173–174
97. Mehra MR (2019) The burden of haemocompatibility with left ventricular assist systems: a complex weave. Eur Heart J. 40: 673–677
98. Mehra M, Naka Y, Uriel N, Goldstein DJ, Cleveland JC Jr, Colombo PC, Walsh MN, Milano CA, Patel CB, Jorde UP, Pagani FD, Aaronson KD, Dean DA, McCants K, Itoh A, Ewald GA, Horstmanshof D, Long JW (2017) Salerno C; MOMENTUM 3 Investigators. A fully magnetically levitated circulatory pump for advanced heart failure. N Engl J Med. 376:440–450
99. Rogers JG, Pagani FD, Tatooles AJ, Bhat G, Slaughter MS, Birks EJ, Boyce SW, Najjar SS, Jeevanandam V, Anderson AS, Gregoric ID, Mallidi H, Leadley K, Aaronson KD, Frazier OH, Milano CA (2017) Intrapericardial left ventricular assist device for advanced heart failure. N Engl J Med. 376:451–460
100. Morshuis M, El-Banayosy A, Arusoglu L, Koerfer R, Hetzer R, Wieselthaler G, Pavie A, Nojiri C (2009) European experience of DuraHeart magnetically levitated centrifugal left ventricular assist system. Eur J Cardiothorac Surg. 35:1020–1027
101. Morshuis M, Schoenbrodt M, Nojiri C, Roefe D, Schulte-Eistrup S, Boergermann J, Gummert JF, Arusoglu L (2010) DuraHeart magnetically levitated centrifugal left ventricular assist system for advanced heart failure patients. Expert Rev. Med Devices. 7: 173–183
102. Mehra M, Kobashigawa J, Starling R, Russell S, Uber P, Parameshwar J, Mohacsi P, Augustine S, Aaronson K, Barr M (2006) Listing criteria for heart transplantation: Inter-national Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates—2006. J Heart Lung Transplant. 25:1024–1042
103. Banner NR, Bonser RS, Clark AL, Clark S, Cowburn PJ, Gardner RS, Kalra PR, McDonagh T, Rogers CA, Swan L, Parameshwar J, Thomas HL, Williams SG (2011) UK guidelines for referral and assessment of adults for heart transplantation. Heart. 97:1520–1527
104. Stehlik J, Edwards LB, Kucheryavaya AY, Benden C, Christie JD, Dobbels F, Kirk R, Rahmel AO, Hertz MI (2011) The Registry of the International Society for Heart and Lung Transplantation: Twenty-eighth Adult Heart Transplant Report–2011. J Heart Lung Transplant. 30:1078–1094
105. Deng MC, De Meester JM, Smits JM, Heinecke J, Scheld HH (2000) Effect of receiving a heart transplant: analysis of a national cohort entered on to a waiting list, stratified by heart failure severity: Comparative Outcome and Clinical Profiles in Transplantation (COCPIT) Study Group. BMJ. 321:540–545
106. Mehra MR, Canter CE, Hannan MM, Semigran MJ, Uber PA, Baran DA, Danziger-Isakov L, Kirklin JK, Kirk R, Kushwaha SS, Lund LH, Potena L, Ross HJ, Taylor DO, Verschuuren EA, Zuckermann A (2016) The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: A 10-year update. J Heart Lung Transplant. 35:1–23
107. Drakos SG, Kfoury AG, Gilbert EM, Horne BD, Long JW, Stringham JC, Campbell BA, Renlund DG (2007) Effect of reversible pulmonary hypertension on outcomes after heart transplantation. J Heart Lung Transplant. 26:319–323
108. Tedford RJ, Hemnes AR, Russell SD, Wittstein IS, Mahmud M, Zaiman AL, Mathai SC, Thiemann DR, Hassoun PM, Girgis RE, Orens JB, Shah AS, Yuh D, Conte JV, Champion HC (2008) PDE5A inhibitor treatment of persistent pulmonary hypertension after mechanical circulatory support. Circ Heart Fail. 1:213–219
109. Loh E, Bergin J, Couper G, Mudge GJ (1994) Role of panel-reactive antibody cross-reactivity in predicting survival after orthotopic heart transplantation. J Heart Lung Transplant. 13: 194–201