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Invasive Treatment in Advanced (Stage-D) Heart Failure

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Abstract

Heart failure is a complex, true pandemic clinical syndrome and is responsible for 5% of hospitalizations globally. Severe heart failure can manifest as two lethal clinical entities: (1) acute cardiac decompensation with cardiogenic shock after large acute myocardial infarction with mortality rates approaching 50% or after cardiac surgery with mortality rates higher than 65% and (2) chronic destructive cardiac remodeling or acute decompensative exacerbations of cardiomyopathies with one-year mortality of approximately 80% (worse than most types of cancer). Interventional therapies aim first to improve symptoms and life expectancy in patients with severe heart failure syndrome, second to prevent left ventricular remodeling, and third to bridge patients to long-term mechanical circulatory support or transplantation. Several treatment options can be used to stabilize patients. In particular, new percutaneous mitral valve interventions and short-term circulatory support devices open up a new temporary treatment area in symptomatic Stage-D heart failure. The durable or curable surgical destination treatment will be only permanent ventricular assist devices or heart transplantation. This chapter focuses on the treatment steps and new approaches in hospitalized Stage-D heart failure patients.

Keywords: heart failure, heart transplantation, ventricular assist device, ECMO, ECLS

At end-stage, any type of cardiomyopathy (CMP) causes a complex clinical heart failure (HF) syndrome, which results from structural and/or functional impairment of ventricular filling or ejection. This dire clinical situation can cause an adverse vicious cycle that is ultimately fatal if not treated by pharmacological or invasive mechanical support or heart transplantation (HTx). Left ventricular functional abnormalities range from normal-sized left ventricle (LV) with preserved left ventricular ejection fraction (LVEF) to severe left ventricular dilatation (LVD) with markedly reduced LVEF. Reduced LVEF is defined as the clinical diagnosis of HF and $LVEF \leq 40\%$, which means a clinic and functional association of systolic and/or diastolic LVD.

Abnormal systolic and/or diastolic functions impair left ventricular contractile and relaxation functions that result in increasing left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV), as well as left ventricular end-diastolic diameter (LVEDD) and left ventricular end-systolic diameter (LVESD), with the alteration of the left ventricular shape from conical form to spherical form. Adverse elevation of preload and afterload results in increasing left ventricular end-diastolic pressure (LVEDP) and left ventricular end-systolic pressure (LVESP). Inadequate unloading is the primary cause of diastolic LVD due to left ventricular overloading, and ineffectual ejection is the primary cause of systolic LVD due to left ventricular overstretching. This LVD induces overpressure behind the LV, which is initially transient but becomes permanent over time. Increasing left atrial pressure (LAP) in acute decompensation of LVD results in pulmonary congestion and pulmonary edema; however, chronic overload causes increasing pulmonary vascular resistance (PVR) and pulmonary hypertension (PHT). Decompensation of the LV and increased right ventricular afterload also impairs the right ventricle (RV) over time. Both preload pressures defined as pulmonary capillary wedge pressure (PCWP) and central venous pressure (CVP) increase during cardiac failure and cause pulmonary and systemic symptoms. Sympathetic stimulation causes a rise of systemic vascular resistance (SVR) that worsens cardiac decompensation due to increased left ventricular afterload. The goals of HF therapy are decreasing both preloads to prevent tissue-congestion, increasing cardiac output (CO) via lowering both afterloads, and improving contractility of both ventricles to increase blood oxygenation and tissue perfusion.

Clinical appearance depends on systolic and/or diastolic ventricular dysfunction, and all treatment strategies are designed according to the HF-classification from Stage-A to Stage-D (**Table 1**). In the twenty-first century, new treatment options have facilitated delay or interruption of this cardiac deterioration and even enabled functional recovery and structural regeneration through corrective anatomic, functional, hemodynamic, and mechanical interventions and clinical medical improvement (**Figure 1**) [1]. Therapeutic and curative percutaneous or surgical treatments should be performed to rescue the damaged heart, and in this way, to recovery the deterioration of the heart and to prevent the development of HF. So, by definition, of left ventricular recovery presupposes that the patient can tolerate a moderate myocardial dysfunction and remain clinically and hemodynamically stable thereafter. Preinvasive therapy is usually implemented in Stage-C HF and consists of medical treatment, home rest, physical activity restriction, and closer medical follow-up.

Stage-D, advanced, end-stage, or refractory HF are various terms used to describe very sick patients (**Table 2**) [2]. Patients with decompensated Stage-D HF should be hospitalized for invasive, aggressive, effective, and interventional treatment combinations [3]. There are clinical clues that may assist clinicians in identifying patients who are progressing toward advanced HF (**Table 3**) [4]. Stage-D patients are those with truly refractory HF who might be eligible for specialized, advanced treatment strategies including mechanical circulatory support (MCS), procedures to facilitate fluid removal, continuous inotropic infusions, other innovative or experimental surgical procedures, or for end-of-life care, such as hospice [5]. After patients' clinical status improves, they will be bridged to destination treatment or HTx. The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) has developed seven

AHA/ACC	Stage-A	Stage-B	Stage-C		Stage-D (end-stage)						
	NYHA class	I	II	III-A	III-B	IV					
		INTERMACS		7	6	5	4	3	2	1	
		STATUS			2	1-B		1-A			
Stage-A:	At high risk for developing HF without structural heart disease										
Stage-B:	Asymptomatic HF with structural heart disease, but without signs or symptoms of HF										
Stage-C:	Symptomatic HF with structural heart disease with prior or current symptoms of HF										
Stage-D:	Refractory end-stage HF despite maximal medical therapy, requiring specialized interventions										
Class I:	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.										
Class II:	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity (e.g., long-distance walking, climbing two flights of stairs) results in symptoms of HF.										
Class III:	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity (e.g., short-distance walking, climbing one flights of stairs) causes symptoms of HF.										
	B: LVEF ≤ 30% and LVEDD ≥ 60 mm and peak oxygen uptake <20 mL/min/kg and stable > 2 months										
Class IV:	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.										
INTERMACS 1:	Cardiogenic shock										
INTERMACS 2:	High dose intravenous inotropic support with/without t-MCS in instable condition										
INTERMACS 3:	Low dose inotropic support with stable hemodynamics										
INTERMACS 4–6:	Stable hemodynamics without intravenous inotropic support										
INTERMACS 7:	Clinical stable										
STATUS 1A:	On the intravenous inotropic and mechanical circulatory support for acute hemodynamic decompensation with/without mechanical ventilation following by continuous monitoring of both ventricular filling pressures, and recertification every 7th day										
	(a) Ventricular assist device (left, right, biventricular) <30 days										
	(b) Total artificial heart										
	(c) Extracorporeal circulatory support with/without oxygenator										
	(d) Counterpulsatile balloon pumping (intra-, extra-, para-aortic)										
STATUS 1B:	On the intravenous inotropic support or ventricular assist device >30 days										
STATUS 2:	Do not meet above criteria (patients on non-intravenous medical treatment at home)										

HF = heart failure; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction.

Table 1. Classification and interrelation of HF.

profiles that further stratify patients with advanced HF, who will be treated with a destination therapy (**Table 4**) [6]. All other causes, which can manifest in severe cardiac decompensation, should be ruled out during diagnosis.

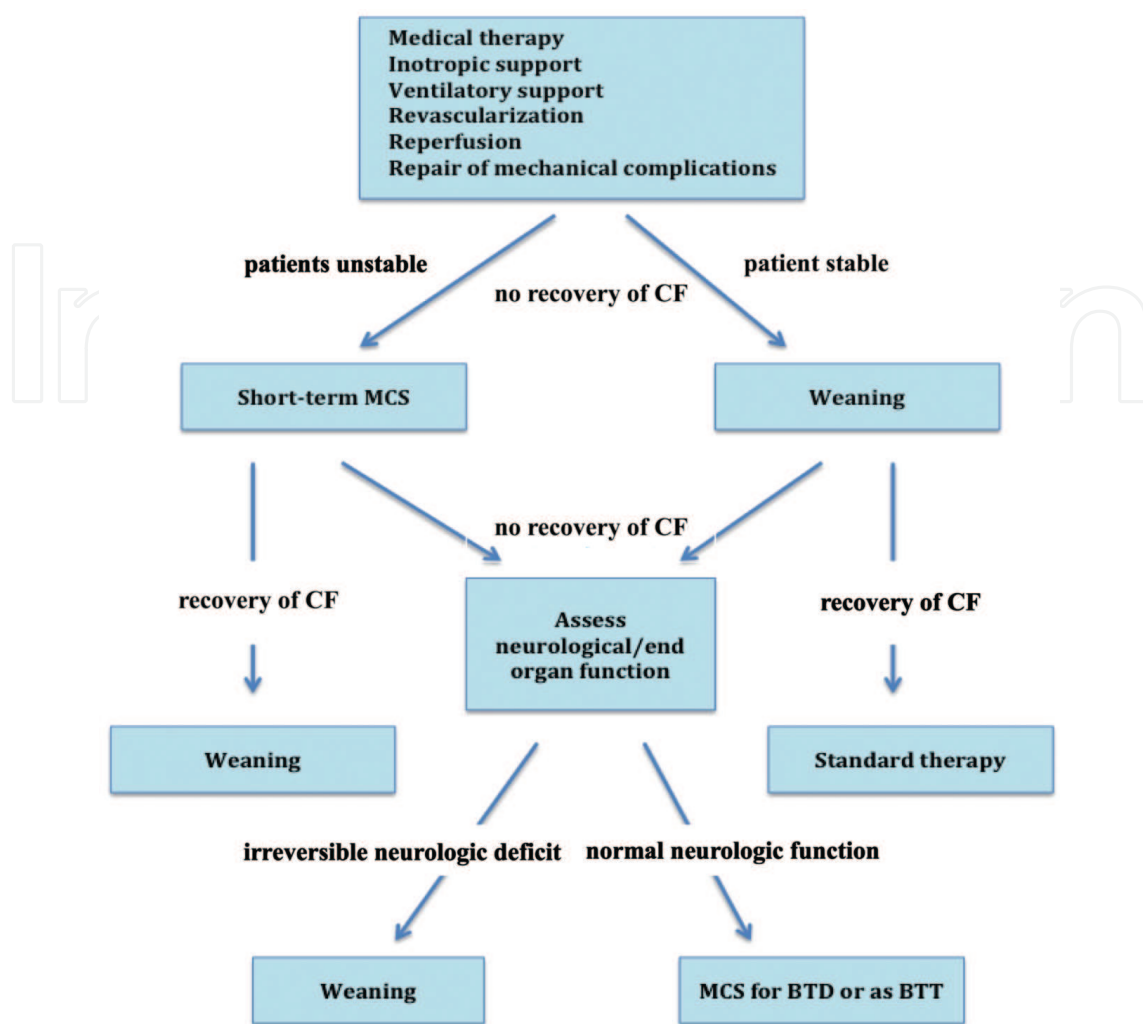


Figure 1. Management algorithm for Stage-D heart failure. BTD = bridge to destination; BTT = bridge to transplantation; CF = cardiac function; MCS = mechanical circulatory support.

Invasive treatments against HF depend on the nature and type of cardiac pathology; however, the systematic approach to their application is well defined (Table 5). The first step is to stabilize the patient's hemodynamics using pharmacological hemodynamic support (PHS), with full intravenous medication including inotropics, vasodilators, inodilators, diuretics, etc. Management of total fluid volume (1.5–2 L/day) and sodium restriction are essential to reduce congestive symptoms, although it is important to avoid hyponatremia by maintaining sodium above 132 mEq/L. Full and continuous monitoring of pre- and afterload (central venous and pulmonary artery catheterization) and CO measurements, echocardiographic examinations (transthoracic and/or transesophageal), and laboratory findings should be implemented in the intensive care unit (ICU). The second step is to carry out any percutaneous interventional support required to eliminate anatomorphologic pathologies (coronary artery stenosis, fibrotic valvular stenosis, etc.) for the purpose of maintaining the satisfactory filling pressures, myocardial contractility, and forward ejection in both circulations. The third and fourth steps apply to patients that are provided with electrical resynchronization and/or mechanical ventilatory support as needed to relieve the negative effects of electromechanical

1. Severe symptoms of HF with dyspnea and/or fatigue at rest or with minimal exertion (NYHA class III or IV)
2. Episodes of fluid retention (pulmonary and/or systemic congestion, peripheral edema) and/or reduced cardiac output at rest (peripheral hypoperfusion)
3. Objective evidence of severe cardiac dysfunction shown by at least one of the following:
 - a. LVEF < 30%
 - b. Pseudonormal or restrictive mitral flow pattern
 - c. Mean PCWP > 16 mmHg and/or RAP > 12 mmHg by pulmonary artery catheterization
 - d. High BNP or NT-proBNP plasma levels in the absence of noncardiac causes
4. Severe impairment of functional capacity shown by one of the following:
 - a. Inability to exercise
 - b. 6-minute walk distance ≤ 300 m
 - c. Peak Vo_2 < 12 to 14 mL/kg/min
5. History of ≥ 1 HF hospitalization in past 6 months
6. Presence of all the previous features despite “attempts to optimize” therapy, including diuretics and GDMT, unless these are poorly tolerated or contraindicated, and CRT when indicated

BNP = B-type natriuretic peptide; CRT = cardiac resynchronization therapy; GDMT = guideline-directed medical therapy; HF = heart failure; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure.

Table 2. Definition of advanced heart failure.

- Repeated (≥2) hospitalizations or emergency department visits for HF in the past year
- Progressive deterioration in renal function (e.g., rise in BUN and creatinine)
- Weight loss without other cause (e.g., cardiac cachexia)
- Intolerance to ACE inhibitors due to hypotension and/or worsening renal function
- Intolerance to beta blockers due to worsening HF or hypotension
- Frequent systolic blood pressure < 90 mmHg
- Persistent dyspnea with dressing or bathing requiring rest
- Inability to walk 1 block on the level ground due to dyspnea or fatigue
- Recent need to escalate diuretics to maintain volume status, often reaching daily furosemide equivalent dose > 160 mg/d and/or use of supplemental metolazone therapy
- Progressive decline in serum sodium, usually to < 133 mEq/L
- Frequent ICD shocks

ACE = angiotensin-converting enzyme; BUN = blood urea nitrogen; HF = heart failure; ICD = implantable cardioverter defibrillator.

Table 3. Clinical events and findings for identifying patients with advanced HF.

Profile	Profile description	Shorthand	Features	IABP	t-MCS*	Hospitalization	Life expectancy	p-MCS**	Timing
1	Critical cardiogenic shock	Crash and burn	Life-threatening hypotension and excessive inotropic/vasopressor support, critical organ hypoperfusion, often worsening acidosis and lactate levels	Yes	Yes	Yes (ICU)	Hours	Emergent (Rescue)	<7 days
2	Progressive decline	Sliding fast	Dependent on inotropic support with/without continuing nutritional depletion, worsening renal function, inability to restore volume balance, or other major status indicator.	Yes	Yes	Yes (ICU/Ward)	Days to weeks	Urgent (salvage)	<30 days
3	Stable, but inotrope-dependent	Dependent stability	Stable blood pressure, organ function and nutrition on mild-moderate doses of continuous intravenous inotropic support after repeated documentation of failure to wean without symptomatic hypotension, worsening symptoms, or progressive organ dysfunction (usually renal).	Yes/no	Yes/no	Yes (Ward)	Few weeks	Elective (destination)	<90 days
4	Recurrent advanced HF	Frequent flyer	Resting and/or daily living activities (dressing or bathing) symptoms of congestion (orthopnea, abdominal discomfort, nausea, poor appetite, disabling ascites, or severe lower-extremity edema), on oral therapy at home,	No	No	No	Weeks to months	Elective (destination)	>90 days
5	Exertion intolerant	House-bound	Comfortable at rest, but unable to engage in any activity, living predominantly within the house or housebound	No	No	No	Weeks to months	Yes/no	?
6	Exertion limited	Walking wounded	Comfortable at rest without evidence of fluid overload and able to do some mild activity, daily living are comfortable and minor activities outside the home, but fatigue results within a few minutes or with any meaningful physical exertion.	No	No	No	Months	Yes/no	No
7	NYHA class III B		Clinically stable with a reasonable level of comfortable activity, despite a history of previous decompensation that is not recent, able to walk more than a block.	No	No	No		No	No

*t-MCS includes IABP, ECMO, ECCS, and others;

**p-MCS includes LVAD, TAH.

HF = heart failure; ICU = intensive care unit; p-MCS = permanent mechanical circulatory support; t-MCS = temporary mechanical circulatory support; NYHA = New York Heart Association.

Table 4. INTERMACS profiles.

-
- (I) Pharmacological hemodynamic support (PHS)
 - (II) Percutaneous interventional support (PIS)
 - 1. Coronary revascularization
 - a. Angioplasty
 - b. Coronary artery bypass grafting on the beating heart (CABG-BH)
 - i. Off-pump
 - ii. On-pump
 - 2. Mitral valve repair
 - a. Percutaneous
 - b. Surgical neo-chordae
 - (III) Electrical resynchronizational support (ERS)
 - (IV) Mechanical ventilatory support (MVS)
 - (V) Mechanical counterpulsatile hemodynamic support (MCHS)
 - 1. Intraaortic counterpulsatile support (IACP)
 - a. Intraaortic balloon pump (IABP)
 - 2. Extraaortic counterpulsatile support (EACP)
 - a. Extra-aortic balloon pump (EABP)
 - 3. Paraaortic counterpulsatile circulation (PACP)
 - a. Paraaortic circulatory device (PACD)
 - b. Pressure-unload left ventricular assist device (PULVAD)
 - c. Kantrowitz CardioVAD (KCV)
 - d. Symphony
 - (VI) Mechanical circulatory support (MCS)
 - 1. Temporary mechanical cardiopulmonary support (t-MCPS)
 - a. Cardiopulmonary bypass (CPB)
 - b. Extracorporeal cardiopulmonary support (ECCPS) or Extracorporeal life support (ECLS)
 - 2. Temporary mechanical circulatory support (t-MCS)
 - a. Extracorporeal circulatory support (ECCS)
 - b. Intracorporeal circulatory support (ICCS)
 - 3. Permanent mechanical circulatory support (p-MCS)
 - a. Ventricular assist device (VAD)
 - b. Total artificial heart (TAH)
 - (VII) Heart transplantation
 - 1. Isolated
-

-
- 2. Heart and lung transplantation
- (VIII) Left ventricular structural restoration
- 1. Aneurysmectomy
 - 2. Cardiomyoplasty
 - 3. Reshaping
 - a. Intracardiac
 - b. Extracardiac
 - i. CorCap Cardiac Support Device
 - ii. Paracor HeartNet Device
-

Table 5. Invasive treatment sequences of the severe end stage heart failure.

dyssynchrony and poor systemic oxygenation. The fifth step entails provision of hemodynamic supports using temporary mechanical circulatory support (t-MCS) devices such as counter-pulsatile circulatory support (CPCS), extracorporeal cardiopulmonary support (ECCPS), or extracorporeal circulatory support (ECCS) to maintain adequate CO for sufficient body perfusion without any congestive sign of the left and/or right HF. The sixth step consists a long-term circulatory support to obtain adequate left with or without right heart circulation for bridging to a destination therapy. The left ventricular assist device (LVAD) and total artificial heart (TAH) are permanent mechanical circulatory support (p-MCS) devices, and for the time being represent the last and best chance to bridge patients to transplantation or destination therapy. The last step is HTx with or without lung(s), which is considered the gold standard for the treatment of refractory Stage-D HF.

1. Pharmacological hemodynamic support (PHS)

Decompensation of Stage-D HF should be treated in hospital immediately, medically, aggressively, intravenously, and with a multidisciplinary approach. Nowadays, we have a lot of pharmacological treatment weapons with contractor, vasodilator, vasopressor, and inactivator effects [7]. Diuretics for congestion, antiarrhythmics for dysrhythmia, anticoagulations for thrombosis, and digoxin for right heart failure are integral parts of medical treatment (**Figure 2**). With the advent of neurohormonal blockade, tremendous progress has been made in the medical treatment of the advanced HF. Treatment of comorbid conditions such as diabetes and iron deficiency can aid clinical recovery.

Inotropic or inodilator therapy is the initial pharmacological strategy to improve myocardial contractility, increase heart rate, reduce afterload through peripheral vasodilatation, and augment CO. Dobutamine and dopamine (inotropic), and milrinone (inodilator) are the three most commonly used intravenous agents.

Dobutamine (2–20 µg/kg/min) is the most used sympathomimetic agent, and its inotropic and chronotropic effects derive from direct stimulation of β₁ adrenergic receptors, which are

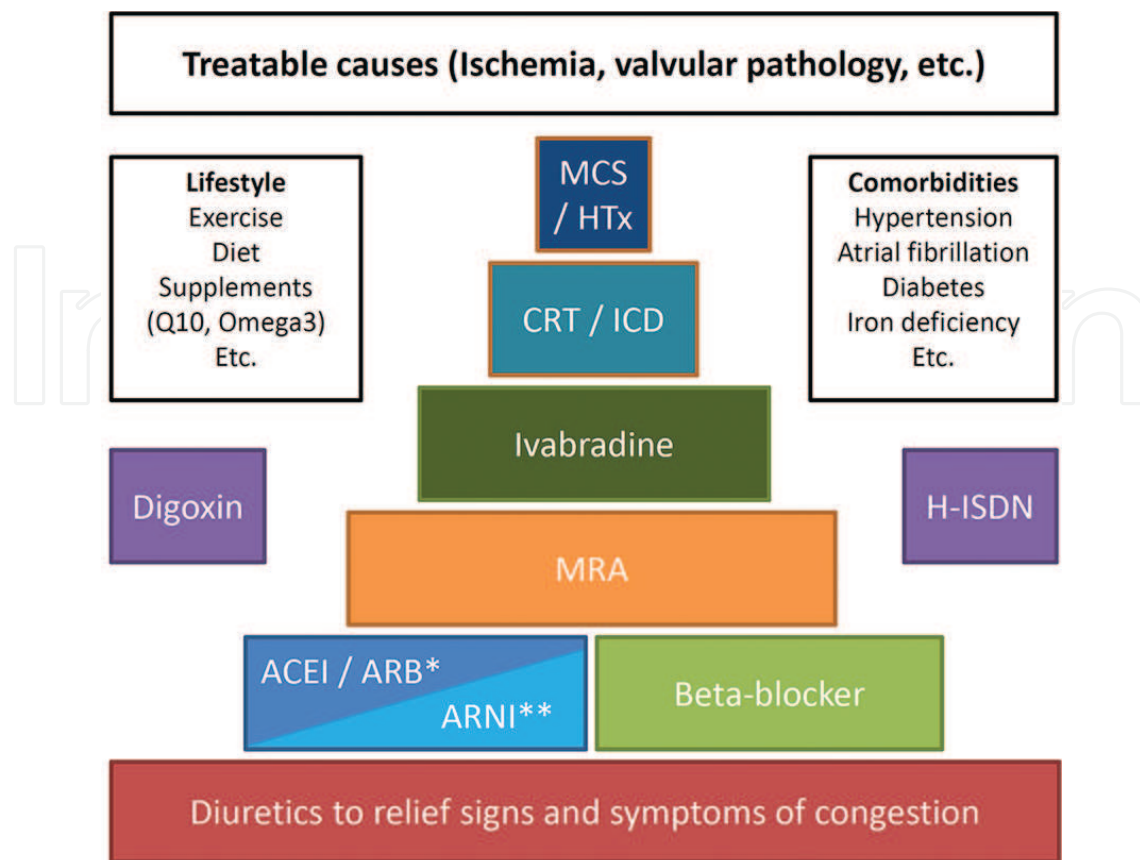


Figure 2. Current therapies for end-stage heart failure. *An ARB is recommended when an ACEI is not tolerated. **An ARNIs is recommended when both RAAS inhibitors are ineffective. ACEI = angiotensin converting-enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; CRT = cardiac resynchronization therapy; ICD = implantable cardioverter defibrillator; H-ISDN = hydralazine-isosorbide dinitrate; HTx = heart transplantation; MCS = mechanical circulatory support; MRA= mineralocorticoid antagonist; omega3 = omega-3 polyunsaturated fatty acids; Q10 = coenzyme Q10.

mostly downregulated in end-stage HF patients. The main effect is inotropic, and it may increase coronary blood flow, but myocardial oxygen consumption can increase if dobutamine induces tachycardia. Tachycardia depends more on dobutamine-related cardiac output than on infusion level.

Dopamine stimulates different receptors depending on dose level: in low (diuretic) doses (0.5–3 µg/kg/min) dopaminergic receptors in the renal, mesenteric, and coronary arterial beds are stimulated; in moderate (inotropic) doses (3–10 µg/kg/min), nonselective adrenergic receptors are activated; in high (vasoconstrictive) doses (>10 µg/kg/min), especially α-adrenergic receptors are induced.

Milrinone (0.25–0.75 µg/kg/min) acts by a nonadrenergic mechanism, increasing c-AMP via phosphodiesterase III inhibition. It is preferred mostly in patients with increased PVR and/or SVR due to better vascular vasodilation than dobutamine. It is crucial to be aware of the risk of systemic hypotension, for which concomitant vasopressors should be added. Milrinone increases CO without increasing overall myocardial oxygen consumption, but does improve myocardial diastolic relaxation (lusitropic effect).

Vasopressor therapy is necessary to increase SVR, blood pressures, and mean arterial pressure, when the low cardiac output syndrome (LCOS) is serious with fairly lower systemic blood pressure. *Adrenalin* (2–10 µg/min or 0.01–0.4 µg/kg/min) is used primarily to maintain cardiac contractility and CO by counteracting bradycardia and hypocontractility. *Noradrenalin* (2–16 µg/min or 0.01–0.3 µg/kg/min) is used primarily to maintain mean systemic arterial pressure by controlling hypotension, severe vasodilatation, or vasoplegia syndrome. It is also an integral part of inodilator treatment modality to prevent systemic vasodilatation.

Vasodilator therapy is needed in most HF patients to decrease SVR and also PVR. Nitroglycerin (10–500 µg/min) and nitroprusside (10–500 µg/min) are the most commonly-used agents in cardiac surgery, but prostaglandins and nitric oxide (NO) more specifically decrease PVR and right ventricular afterload in patients with end-stage HF due to the improvement of the right ventricular dysfunction (RVD) and CO. Long-term therapy with sildenafil has demonstrated better hemodynamics in lowering PVR. In addition, endothelin receptor antagonists, such as bosentan, can also be used although they are not currently included in treatment guidelines.

Diuretics restrict the reabsorption of sodium in the renal tubes, increase urinary sodium excretion, and decrease congestive symptoms in HF patients. Loop diuretics (furosemide, bumetanide, torsemide) are preferred pharmacological agents in hospitalized patients and used intravenously. The first goal is to resolve fluid retention and congestive signs (edema, hepatomegaly, pulmonary edema, etc.), and then to prevent the recurrence of volume overload. The most common side effects of excessive diuretic usage include fluid depletion, hypokalemia, hypomagnesaemia, and azotemia. Furosemide is the most common used loop diuretic, the dose and frequency should be increased until the adequate diuresis and weight loss is maintained. Low-dose dopamine (2 µg/kg/min) infusion can improve diuresis and better preserve renal function. If the diuretic strategy is unsatisfactory or ineffective due to renal failure, ultrafiltration to remove water and small- to medium-weight solutes may be considered as a primary volume-removal therapy. After acute decompensation caused by volume overload resolves, oral diuretic therapy is started with furosemide and/or thiazides and spironolactone combination. Daily recording of body weight is the best parameter to follow diuretic treatment's effectiveness and to adjust dosage.

Renin-angiotensin-aldosterone system (RAAS) is at the core of the pathophysiology of HF, and its modulation is central to altering the disease process in HF with reduced LVEF. Blockade of RAAS can be provided by an angiotensin-converting enzyme inhibitor (ACEI), angiotensin-receptor blocker (ARB), or mineralocorticoid receptor antagonist (MRA). This inhibition can reduce blood pressure in hypertensive patients, prevent target organ damage in diabetes, and improve outcomes in HF patients [8]. This hormone system regulates protective acute stress response through inflammatory and proliferative mechanisms; however, chronic stimulation has detrimental effects including vasoconstriction, sodium and water retention, vascular smooth muscle proliferation, endothelial dysfunction, inflammation, fibrosis, and thrombosis [9]. The RAAS cascade begins with renin secretion by renal juxtaglomerular cells, continues with the conversion of hepatic angiotensinogen to the inactive angiotensin I, and finishes with conversion of angiotensin I to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II is the strongest mediator to promote all effects above mentioned, and it stimulates the

secretion of aldosterone from adrenal cortex and arginine vasopressin from posterior pituitary. Blockade of the RAAS with ACEIs has been a cornerstone of HF therapy for over 20 years, so that ACEIs decrease the formation of angiotensin II and inhibit the breakdown of bradykinin with the formation of NO and other vasodilators. Additionally, further blockade of RAAS with aldosterone antagonists and ARBs has increased the efficiency, so that ARBs bind competitively to and dissociate slowly from angiotensin type-1 receptors and blockade aldosterone secretion. MRAs cover mineralocorticoid receptors for competitive inhibition. The direct renin inhibitor (DRI) agents blockade the RAAS at the most proximal step via the inhibition of angiotensinogen conversion.

Natriuretic peptide system (NPS) counter regulates the detrimental effects of the up-regulation of RAAS, inhibits secretion of arginine vasopressin, modulates the autonomic nervous system, and antagonizes their vasopressor effects in HF [10]. There are three peptides: atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and endothelial cell natriuretic peptide (CNP). Both ANP and BNP have similar structural, hypotensive, natriuretic, and diuretic properties. Distension of the atria and ventricles due to cardiac injury and/or overload, ventricular dysfunction, and HF stimulates the expression of ANP from atria and BNP from brain and ventricles with several effects: (1) activation of membrane-bound natriuretic peptide receptors-A leading to vasorelaxation, natriuresis, and diuresis; (2) inhibition of RAAS due to blocked of renin secretion and associated aldosterone production; (3) reduction in adverse cardiovascular changes via remodeling, apoptosis, ventricular hypertrophy, and fibrosis; and (4) enhanced myocardial relaxation. On the other hand, CNP extracted from endothelial cells and brain acts only as a vasodilator without potent diuretic and natriuretic effects. Measurements of peptides ANP, BNP, and its inactive precursor N-terminal fragment of pro-B-type natriuretic peptide (NT-proBNP) are useful in prognosis assessment and antifailure therapy monitoring, but CNP is not measurable due to low concentrations in circulating blood. Natriuretic peptides are removed from circulation through two mechanisms: clearing by natriuretic peptide clearance receptor (NPRC and NPRC3) or inactivating by a degrading enzyme. The endothelial enzyme *neprilysin* hydrolyzes ANP rapidly and also degrades a large number of other vasodilators and vasoconstrictors although BNP is relatively resistant to its digestion. Inhibition of neprilysin (NEPi) with *sacubitril* (1) increases concentrations of circulating vasodilators (ANP, adrenomedullin, and bradykinin), but also circulating vasopressors (angiotensin II, endothelin I); (2) augments plasma ANP and BNP levels leading to enhanced natriuretic-diuretic-vasodilator effects, lower preloads, and inhibition of fibrosis; (3) inhibits renin secretion and angiotensin I to II conversion, but that is not a complete inhibition effect on the RAAS. However, blocking neprilysin alone does not effect a complete inhibition of RAAS, which is stimulated by the activated sympathetic nervous system (SNS) leading to increasing renin secretion and ACE activation of angiotensin I to II. These opposing effects neutralize each other and therefore NPS inhibitors alone exert little effect on hemodynamics. This problem is solved by dual blockade of RAAS by ARB and NPS by NEPi. The combined molecule of sacubitril (NEPi) and valsartan (ARB) is a first drug (LCZ696) in class angiotensin receptor neprilysin inhibitor (ARNi), and represents a new treatment modality by blocking the angiotensin type-1 receptor and inhibiting the natriuretic peptide system concurrently [11]. Valsartan does not inhibit

the breakdown of bradykinin, with decreasing angioedema risk; however, inhibition of angiotensin II action prevents vasopressor effects. This combination favors NPS activation and RAAS blockade, as well as residual angiotensin II effects from the SNS [12].

Digoxin is the oldest cardiac drug still in contemporary use, and can be useful in patients with persistent severe end-stage HF (LVEF <25%, cardiothoracic ratio >55%, New York Heart Association (NYHA) class III or IV) undergoing guideline-directed medical therapy, and especially symptomatic patients being treated with neurohormonal antagonists [13]. Digoxin has been used as the first line of pharmacological treatment for HF until the understanding of HF pathophysiology changed in recent decades, which leads to the shift from inotropic support to neurohormonal modulation [14]. The effect is regardless of the rhythm, etiology of HF, or concomitant therapy. Digoxin binds for the sarcolemmal $\text{Na}^+\text{-K}^+\text{-ATPase}$ pump to blocking and impeding Na^+ extrusion outside, accumulated intracellular Na^+ decreases the transmembrane sodium gradient, and as a consequence suppresses the activity of the $\text{Na}^+\text{-Ca}^{++}\text{-exchanger}$, raising the intracellular Ca^{++} concentration and effecting more forceful contraction. Digoxin is the only inotrope known to improve LVEF and CO and also to reduce PCWP without tachycardia and/or hypotension. The beneficial effect of the drug occurs even at low maintenance dosage (serum digoxin concentration 0.5–0.9 ng/mL; 0.125 mg/day) with positive inotropic but negative chronotropic (4–7 beats/min in sinus rhythm) properties. The hemodynamic effects of digoxin are not attenuated by chronic administration, because $\text{Na}^+\text{-K}^+\text{-ATPase}$ is not upregulated. In noncardiac tissue, digoxin acts as a neurohormonal modulator by increasing parasympathetic tone and dampening activation of the SNS (sympatholytic) and RAAS.

2. Percutaneous interventional support (PIS)

Cardiac decompensation is usually a consequence of myocardial ischemia and/or mechanical complications, or chronic remodeling. Acute HF develops after ischemic damage or acute hemodynamic compromise of chronic HF with well-known structural pathologies during medical follow-up. These patients may not improve with medical therapy; however, correction of underlying pathologies such as coronary artery disease, valvular stenosis, or regurgitation can result in significant improvement in functional status. Before mechanical circulatory treatments, all applicable interventional therapies must be evaluated and performed confidentially. First of all, percutaneous revascularization is the initial step in managing inadequate oxygen delivery due to stenotic or occluded coronary arteries, and that must be followed by percutaneous palliative mitral valve repair if it is necessary. Significant mitral regurgitation (MR) resulting in inadequate forward ejection of the LV can cause intractable left heart failure (LHF), even if total stroke volume seems enough to produce adequate CO. The goal of palliative percutaneous interventions for these pathologies is to maintain and sustain adequate left ventricular filling and forward ejection. If these treatment strategies are successful, patients have the chance to get better and postpone mechanical hemodynamic and/or circulatory support; however, inoperable or untouchable patients should be considered for destination therapy.

2.1. Coronary revascularization

Ischemic myocardium or acute coronary syndrome decreases significantly ventricular contractile function due to oxygen supply/demand imbalance. Hibernating, stunning, or infarction reduces LVEF, causes left ventricular remodeling, and exacerbates mitral valve dysfunction. Coronary angiography shows stenotic or occluded coronary territory, but stress echocardiography, nuclear imaging, and magnetic resonance imaging examinations show whether there are viable tissues and/or valvular dysfunction requiring corrective interventions, as well as for surgical treatment despite higher procedural risks. Coronary revascularization can salvage and improve the myocardium histologically and functionally, but these strategies usually fail to improve myocardial recovery due to nonviable myocardium.

2.1.1. Angioplasty

Any severe atherosclerotic plaque, plaque rupture, or thrombotic occlusion reduces oxygen delivery to the myocardium, which results acute LHF. Persistent angina is also a common symptom (approximately 30%) in patients with ischemic CMP despite medical therapy, which increases major cardiac events by one third [15]. Percutaneous coronary intervention via balloon angioplasty associated with or without stent implantation is the first-stage therapy for coronary artery disease causing severe cardiac decompensation due to massive ischemia in high-risk patients with well-known compensated HF associated with or without mechanical complications of myocardial infarction, particularly MR. Coronary revascularization could aid in recovery of myocardial dysfunction if the affected myocardium consists of viable tissue, and MR may also be improved. Myocardial reserve after angioplasty also results in contractile improvement and favorable left ventricular remodeling in patients with LVD, and it also decreases HF symptoms (angina, functional class, BNP levels) [16, 17]. Partially or fully viability or transmural scar within the infarct should be identified by any test (scintigraphy, magnetic resonance, etc.) in this group of patients, because improvement in oxygen supply will abate ischemia burden [18, 19]. Transmural distribution of the postinfarction scar, which spreads from the subendocardium to the subepicardium without intermittent viability, does not provide any benefit by angioplasty. Although surgical coronary revascularization is superior to medical therapy in patients with HF [20], there is no real superiority of surgery over angioplasty [21]. Contrarily, the positive benefit of percutaneous revascularization of the viable region is a significant improvement in the LVEF and LVESV in the LHF patients. New designed clinical trials will give more detailed results regarding angioplasty performed in HF [22]. Unstable or hemodynamically instable patients with significant HF symptoms must be undertaken in catheter laboratory with a t-MCS to prevent sudden decompensation or cardiac arrest. The most preferable device to maintain adequate CO during percutaneous procedures is intraaortic balloon pump (IABP), which can be supported or replaced by a percutaneous temporary device (Impella, TandemHeart, etc.).

2.1.2. Coronary artery bypass grafting

Patients with severe HF and coronary artery disease suitable for coronary artery bypass grafting (CABG) are at higher risk for surgical morbidity and mortality. Paradoxically, those

patients who derive the greatest clinical benefit from CABG and are also at the greatest operative risk, which leads clinicians to hesitate to refer these patients for CABG [23]. Despite the fact that bypass surgery can create potential risks for HF patients, significantly viable tissue should be revascularized by on- or off-pump CABG [24]. Minimal invasive CABG procedures are an option, but dilated left ventricular cavity with or without right ventricular enlargement complicates off-pump CABG due to hemodynamic instability during the elevation of the heart for circumflex or right coronary artery anastomoses [25]. Single vessel bypass to the dominant left anterior descending territory can be useful in symptomatic multivessel disease patients, and this approach can cause a limited improvement in the LVEF and clinical status [26]. But, in the case of unsuitable pathology and anatomic structure of the coronary artery territory, viable tissue should be identified before surgery. Single coronary artery revascularization could be performed percutaneously or off-pump surgically [27]. On-pump CABG could be more harmful due to aortic cross clamping, but enrichment of cardioplegia with different agents may be protective [28].

2.2. Mitral valve repair

Functional MR due to LVD and remodeling is a common complication in dilated or ischemic CMPs, and severe symptomatic MR requires an invasive corrective intervention to prevent poor prognosis and to improve clinical status. However, the effectiveness of repair of MR in these situations is often compromised because it does not reverse the underlying cause of the CMP. While surgical mitral valve repair is the conventional treatment for MR, it is controversial in end-stage HF patients due to high surgical risk and lack of randomized trials about survival benefit. Because severe functional MR clearly increases the mortality as an independent predictor but mitral valve repair does not improve mid- and long-term survival in patients with end-stage HF, most major guidelines recommend against isolated mitral valve surgery in these patients, although surgery is generally recommended if aortic valve or coronary artery bypass graft surgery is also being performed [29]. Ideal candidates should have less fibrotic spherical ventricle with more contractile reserve, patients with irreversible pulmonary hypertension and severe right ventricle dysfunction would be unlikely to benefit from intervention [30]. Transcatheter mitral valve repair or implantation alternatives are currently preferred in high-risk patients not eligible for surgery [31]. Percutaneous mitral valve implantation seems to be the best solution to eliminate MR in end-stage HF patients with significant MR caused by severe annular enlargement [32].

2.2.1. Percutaneous mitral valve repair

Newly developed percutaneous mitral valve repair techniques can be useful in patients, who cannot be referred for surgical therapy (**Table 6**) [33]. In contrast to the positive effect of percutaneous mitral valve repair techniques in patients with severe MR-associated nonfailed hearts, mitral valve repairing is offered without targeting of full coaptation of mitral valve in end-stage HF patients. It is usually anatomically impossible to fully repair the mitral valve completely due to severe annular enlargement and/or the tethering of the leaflets caused by left

Percutaneous mitral valve repair	
Leaflet	
Edge-to-edge (leaflet plication)	MitraClip
	MitraFlex
Space occupier (leaflet coaptation)	Percu-Pro
Leaflet ablation	Thermocool
Annulus	
<i>Indirect approaches</i>	
Coronary sinus annuloplasty	Carillon
	Monarc
	Viacor
Asymmetrical approach	St Jude annulus reshaping device
	NIH-cerclage technology
<i>Direct approaches</i>	
Percutaneous mechanical cinching	Mitralign suture-based plication
	Accucinch GDS millipede ring system
Percutaneous energy-mediated cinching	QuantumCor
	ReCor
Hybrid	Mitral solution
	MiCardia
Chordal implants	
Transapical artificial chord	NeoChord
	MitraFlex
Transapical-Transseptal	Babic
Left ventricle	
LV remodelling	Mardil-BASE
	iCoapsys
Percutaneous mitral valve implantation	
Right mini-thoracotomy	Endo valve-Herrmann prosthesis
Transapical	Lutter prosthesis
Transseptal	CardiaQ prosthesis

Table 6. Percutaneous mitral interventions.

ventricular enlargement, as well as it can be very devastating for failed hearts. Therefore, percutaneous mitral valve repair techniques are palliative, but also preparative interventions to improve patients' clinical status and hemodynamics before destination therapies like LVAD or HTx.

The MitraClip is a novel technology for percutaneous treatment of MR, although its utility in patients with end-stage HF is somewhat limited [34]. This leaflet plication technology is based on the surgical Alfieri technique, which brings the anterior and posterior leaflets together with a suture, creating a “double orifice” mitral valve. The device is inserted by way of the femoral vein and utilizes a 24F guidewire to gain transseptal access to the left atrium (LA). It is essential to place the V-shaped clip at the main MR site between the anterior and posterior leaflet with the guidance of transesophageal echocardiography. The first clip may not solve the problem, but decreases degree of regurgitation from massive to severe or moderate-severe, and additional clip(s) could be applied to significantly reduce degree of regurgitation to moderate or lower. At least 50% reduction in the MR performed by mitral clips could be accepted as a successful procedure, while more than 75% without mitral stenosis could cause effective correction. This new device has shown benefit in outcomes for patients without HF, but it is unable to improve the clinical course in end-stage HF patients due to an immediate deterioration of left ventricular function, further aggravation of afterload mismatch, and progressive LHF [35]. MitraClip is a good alternative to surgery in functional MR refractory to medical and/or resynchronization therapy in patients with adequate anatomy, but not in patients who are considered inoperable due to high surgical risks [36]. It can be considered an important clinical option in the multidisciplinary treatment of HF, but postprocedural MR increases midterm cardiac mortality [37]. To increase utilization of the MitraClip treatment, this new approach must be used in selective cases or as an earlier step before the destination therapy. The first 30 days have an acceptable course, but after that the frequency of adverse events increases, especially early recurrence/persistence of MR [38].

The Carillon is a percutaneous coronary sinus-based mitral annuloplasty device designed to treat functional MR in end-stage HF patients [39]. This device consists of self-expandable nitinol distal and proximal anchors connected by a nitinol bridge, which are placed in the great cardiac vein and proximal coronary sinus located behind the posterior mitral annulus. Tension applied on the system results in cinching of the posterior periannular tissue, and displacement of the posterior mitral leaflet toward the anterior leaflet to reduce anterior-posterior (septal-lateral) dimension improves their coaptation and reduces functional MR [40]. Residual MR is not frequently observed in patients without HF, and it can decrease significantly in the first 3 months [41]. However, LVD associated with significant mitral annular enlargement results in significant MR, but also, mitral valve tethering complicates MR. This pathologic course could not be reversed completely by percutaneous mitral annuloplasty devices. This technique reduces functional MR significantly, increases functional capacity and quality of life, as well as induces improvement of left ventricular remodeling [42]. The major limitations to use this kind of devices are the significant distance between coronary sinus and mitral annulus, closed anatomic neighborhood of coronary arteries, and annular calcifications.

2.2.2. *Surgical mitral valve repair*

Surgical mitral valve correction is seldom preferred because of the high risks associated with the operation. On-pump surgery is usually not recommended, and severe MR with clinical deterioration can be the first indication for LVAD implantation. Transapical

correction using NeoChord has been popularized in degenerative MR, and the new devices facilitate transapical implantation of neo-chordae on the beating heart without cardiopulmonary bypass (CPB) [43]. This approach is useful in isolated mitral valve leaflet(s) prolapse with lower operative risk [44]. However, no high-quality studies have investigated the possibility of implantation in severe HF situations with LVD and mitral leaflet tethering. This approach could be preferred in severe MR caused by chordal rupture without adding of ring annuloplasty. However, patients with a LVD and a significant MR have significant mitral annular dilatation without mitral valve prolapses, and in such cases MR can be corrected only via a prosthetic ring percutaneously. Otherwise, severe HF associated with significant MR is one of the best candidates for LVAD destination therapy.

3. Electrical resynchronizational support (ERS)

Electromechanical dyssynchrony is common in end-stage HF patients and can be found at different levels within the heart. Electrical dyssynchrony is evidenced by QRS prolongation (≥ 120 ms) and has a prevalence of 15–30% in HF population. Electrical dyssynchrony, and the subsequent abnormal mechanical activation, results in cellular, structural, hemodynamic, and ultimately clinical adverse effects [45]. Left bundle branch block results in a shorter diastolic time interval and longer isovolumetric contraction and relaxation times, which impair pump function because of abnormal electrical and mechanical properties, as well as functional MR. These effects can be ameliorated by resynchronizing the failing heart by means of pacing in the right atrium (RA) and both ventricles (biventricular pacing). Cardiac resynchronization therapy restores the appropriate timing of the cardiac contraction pattern and thereby not only reduces cellular, hemodynamic, and structural maladaptations to dyssynchrony, but also ultimately improves functional status, reduces hospitalization, and improves survival.

4. Mechanical ventilatory support (MVS)

Even when cardiac dysfunction is the only reason for HF syndrome, increased PVR raises respiratory effort and increased SVR reduces systemic output, decreasing pre- and afterload and increasing oxygenation, which results hemodynamic stability. The most common supportive approach in end-stage HF patients with respiratory failure is mechanical ventilation under general anesthesia. Intubation is usually the first step to maintain hemodynamic stability through decreased respiratory effort and adrenergic stimulation. Increasing oxygenation and use of vasodilator inhalation decrease adverse responses and PVR, which is the main treatment strategy for the right ventricular failure (RVF). Supportive mechanical hemodynamic approaches prevent unnecessary and prolonged mechanical ventilation, which can be a significant risk factor for ventilator-dependent infections. Elective intubation is also required for percutaneous mitral valve repair.

5. Mechanical counterpulsatile hemodynamic support (MCHS)

In severe cases of decompensated HF, pharmacological hemodynamic support cannot usually achieve complete hemodynamic stability and maintain adequate blood supply to end-organs and tissues in the decompensated HF. End-stage HF patients with severe ventricular decompensation are frequently referred to ICUs for hemodynamic support. After full monitoring and assessment of hemodynamic parameters, the required appropriate medications are used to solve symptoms and signs of LCOS; however, full medication can heal patients for once, but then healing degrades and pharmacologic bridge to transplantation cannot stabilize patients, and hence mechanical counterpulsatile hemodynamic support (MCHS) becomes necessary.

5.1. Intraaortic counterpulsatile support (IACPS)

Counterpulsatile devices for MHS improve patient status by same physiologic effects, but with different mechanisms (Table 7) [46]. The principle of counterpulsation is to produce diastolic augmentation. Prediastolic inflation coincided with T-P interval on electrocardiogram provides increase in peak diastolic aortic pressure (aortic uploading) to enhance coronary perfusion during ventricular relaxation and filling. Presystolic deflation coincided with QRS-T interval on electrocardiogram, which is always triggered by R wave, assures decreasing in end-diastolic aortic pressure (aortic unloading) to facilitate intraaortic impedance reduction during ventricular contraction and ejection. These devices are usually used for short-term supportive therapy in early postoperative period to wean patients from CPB. There are several positive effects of counterpulsation on systemic hemodynamics and left ventricular mechanoeenergetics, but the main goal is to increase CO without bypassing the heart or the related ventricle [47]. Second application area in end-stage HF patients is to stabilize hemodynamics and to gain time for keeping patients alive or bridging to a more durable therapy. The first step

	Intraaortic	Paraaortic
Insertion	Percutaneously	Surgically
Incision	Sliding technique or local incision	Intraoperatively or left thoracotomy
Placement way	Peripheral	Semicentral
Placement area	Suprarenal thoracoabdominal aorta	Thoracal descending aorta
Capacity	30–50 mL	20–100 (or more) mL
Working principle	Volumetric	Circulatory
Working space	Intraluminal	Extraluminal
Working risk	Systolic occlusive	Nonocclusive
Inflation/deflation	Diastole/systole	Diastole + systole
Coronary perfusion	Optimum/steal	Optimum
Stroke work	Decreasing (+)	Decreasing (+++)
Cardiac output	Increasing	Increasing

Table 7. Comparison of counterpulsatil devices.

is to stabilize the end-stage HF patients using IABP for up to 2 weeks and if the patients are hemodynamically stabilized (no need for inotropes, no peripheral organ malfunction, CVP \leq 10 mmHg, mean arterial pressure \geq 65 mmHg) but could not wean from IABP, then they can be transitioned to a more effective counterpulsatile or t-MCS devices as a bridge to recovery or to end-stage therapy (p-MCS device or HTx).

Intraaortic balloon pump (IABP) is the most preferred, well-tolerated, and most cost-efficient method among mechanical supportive approaches with significant hemodynamic improvements in patients with unstable hemodynamic status (**Table 8**) [48]. But the frequency of IABP

-
- (I) Therapeutic
 - A. Preoperatively
 - 1. Unstable myocardial ischemia
 - a. acute coronary syndrome
 - b. intractable coronary ischemia
 - c. severe left main disease
 - d. malign ventricular arrhythmia
 - 2. Cardiogenic shock
 - a. myocardial infarction
 - b. mechanical complications of AMI (MR, VSD, LVR)
 - c. myocarditis
 - d. sepsis
 - 3. Cardiomyopathies
 - 4. Procedural support during coronary angiography
 - 5. Stabilization for surgery
 - a. cardiac surgical patients (LCOS, VSD, severe MR)
 - b. noncardiac surgical patients
 - B. Intraoperatively
 - 1. Off-pump CABG
 - 2. On-pump CABG on the beating heart
 - 3. LVAD implantation
 - C. Postoperatively
 - 1. Failure to separate from CPB
 - 2. LCOS
 - (II) Bridging
 - A. Heart transplantation
 - B. Left ventricular assist device
-

	C. Total artificial heart
(III)	Diagnostic
	A. Reversibility of pulmonary (PAH, PVR)

AMI = acute myocardial infarction; CABG = coronary artery bypass grafting; CPB = cardiopulmonary bypass; IABP = intraaortic balloon pump; LCOS = low cardiac output syndrome; LVAD = left ventricular assist device; LVR = left ventricular rupture; MR = mitral regurgitation; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; VSD = ventricular septal defect.

Table 8. Indications for IABP.

usage in the end-stage HF patients has broadened in last decade due to the increase in the usage of t-MCS devices to bridge to HTx or LVAD implantation. The main indications for IABP are to increase myocardial perfusion in critical uncontrolled coronary artery stenosis preoperatively and to improve CO in severe LHF postoperatively [49]. The purpose of this indication is to decrease afterload and consequently to facilitate unloading of the LV, especially LHF complicated with significant MR. Intraaortic balloon pumping relies on the principle of diastolic counterpulsation, which causes a reduction in left ventricular afterload and an increase in aortic diastolic and consequently coronary artery perfusion pressures. Because the descending aorta has a particular diameter the balloon catheter should have a limited volume, which are two types for adults: 40 mL (26 cm length and 1.5 cm diameter) and 50 mL (27 cm length and 1.8 cm diameter). Even the hemodynamic effect of this capacity affects the myocardial oxygen supply/demand ratio favorably due to the decreasing peak systolic wall stress and contractile work of the LV, the net effect will be an increase in forward LVEF, CI, and CO (**Table 9**). However, when IABP support has only limited positive impact on cardiac hemodynamics, it cannot maintain adequate cardiac output in patients with decompensated severe left HF or reduce clinical symptoms and hemodynamic signs. In such cases, this hemodynamic supportive strategy must be complemented by more advanced MCS devices [50].

Therapeutic usage of IABP is well known and accepted treatment strategy to reverse or prevent moderate LCOS owing to hibernating or stunned myocardium after acute coronary syndrome, during percutaneous cardiac interventions, along malign ventricular arrhythmias, and after mechanical complications of myocardial infarction [51]. High-risk patients undergoing cardiac operations may be also protected against adverse outcomes [52, 53]. Pharmacological and mechanical hemodynamic supports remedies pre- and afterload deterioration through improved CO, coronary perfusion, and improved end-organ perfusion. The latter effect is the main curative treatment strategy to terminate and reverse organ dysfunctions, which increase pre- and postoperative mortality and morbidity. The significant life-saving benefit of IABP support on the early mortality is well known; however, the benefit on either 30-day or 1-year all-cause mortality is dubious in end-stage HF patients due to insufficiency to achieve and sustain adequate CO. Therefore, a more effective MCS device should be utilized if IABP could not achieve adequate CO in a couple of days (<7 days) or immediately when any decompensation develops on the IABP treatment.

Prophylactic long-term usage of counterpulsation to optimize cardiac output and RV function as a bridge to HTx or long-term LVAD implantation is a growing area of application (**Table 10**) [54].

Decrease

Systolic blood pressure	up to 10%
Presystolic aortic pressure (afterload)	up to 30%
LV systolic pressure (wall tension)	up to 20%
Isometric phase of LV contraction	
LV energy utilization (myocardial oxygen consumption; TTI)	
LVEDV + LVEDP (preload)	
PCWP	

Increase

Diastolic blood pressure	
LV mechanical performance	
EF	up to 5%
CI	up to 20%
CO	up to 30% (0.5-1 L/min)
LV energy obtainment (myocardial oxygen supply; DPTI)	
Endocardial Viability Ratio improvement (<0.7 indicates severe myocardial ischemia)	DPTI/TTI > 1
LV contractility and active relaxation	
Coronary blood flow	
Cerebral, renal, mesenteric, and pulmonary blood flow	
Mean arterial pressure (in shock)	

CI = cardiac index; CO = cardiac output; DPTI = diastolic pressure time index; EF = ejection fraction; LV = left ventricular; LVEDP = left ventricular end-diastolic pressure; LVEDV = left ventricular end-diastolic volume; PCWP = pulmonary capillary wedge pressure; SV = stroke volume; TTI = tension time index.

Table 9. Effects of counterpulsation on hemodynamics mechanoenergetics.

Predestinative usage of IABP improves and stabilizes clinical status of potential recipients suffering from multi-organ hypoperfusion and ischemia, which are significant predictors for adverse outcome after HF surgery, to obtain good postoperative results [55]. Prophylactic IABP implementation decreases left ventricular preload and therefore RV upload, which could

Outcome	Recovery	Destination
Bridge to recovery (BTR)	Biventricular or left ventricular	Discharge
Bridge to candidacy (BTC)	Bi- or univentricular	Additional mechanical interventions
Bridge to destination (BTD)	Right ventricular	LVAD
Bridge to transplantation (BTT)	None	Heart ± lung transplantation

IABP = intraaortic balloon pump; LVAD = left ventricular assist device.

Table 10. Potential outcomes of long-term IABP support in chronic heart failure.

terminate hepatic congestion and dysfunction. On the other hand, IABP support improves renal and gastrointestinal blood supply with significant recovery of dysfunctional organs [56]. This strategy can reduce HF symptoms, signs, and laboratory findings (serum total bilirubin and creatinine, plasma BNP levels), especially in the first 48 hours significantly. The most important point is the optimal timing of IABP insertion, which must be earlier as possible, before end-organ dysfunction exceeds the threshold of reversibility, and prophylactic usage must be continued for a minimum of 2 weeks to get effective results. However, long-term IABP support can cause several major complications including acute limb ischemia, severe bleeding, embolic events, infection, and sepsis. When IABP support could not sustain and/or maintain stable hemodynamics, it should be enhanced by implementing more durable devices.

Diagnostic usage is a controversial strategy that could present a significant, favorable alteration in pulmonary arterial pressure and PVR. This improvement could facilitate decisions regarding LVAD implantation or HTx in end-stage HF patients with moderate PVR (6-8 Woods). These patients are not considered to be ideal candidates for HTx according to the guidelines, but they must be investigated whether they could be eligible for initial or postimplant (after LVAD) HTx, or just for destination therapy. More effective left ventricular unloading via IABP also decreases LVEDV, which is the main stimulator for reducing pulmonary venous and consequently pulmonary arterial pressure, and effects a significant reduction in PCWP and CVP initially, as well as in creatinine and total bilirubin concentrations. Two-week application is necessary to see reversibility of PVR, because the positive effect of IABP could be negatively balanced or withdraw after the first week. In this case, PVR will not improve after heart transplant, and mid-term outpatient pharmacologic (sildenafil) and/or mechanical (LVAD) PVR-lowering therapy will be the preferred strategy, with follow-up re-catheterization after 3–6 months to evaluate PVR. Adequate reduction in PVR (<6 Woods) makes these patients potential candidates for HTx. If reduced PVR is sustained, patients will be included in urgent waiting list for HTx (Status 1B) without any additional criteria.

Support with IABP is started after standard maximal pharmacological thresholds (adrenalin or noradrenalin $>0.15 \mu\text{g/kg/min}$) fail to restore hemodynamic stability. The balloon catheter is usually passed percutaneously into the descending thoracic aorta through the femoral artery, but alternative routes, such as the axillary, the subclavian, or the brachial arteries, can be preferred if the femoral artery is not suitable for usage, as well as the ascending aorta could be preferred surgically [57]. Support with IABP is not a complication-free procedure and the most common complications are peripheral arterial injuries (rupture, perforation, bleeding, dissection, embolism, etc.), which is best avoided by sliding technique under ultrasonographic visualization, or complications of distal tissue malperfusion (extremities' ischemia), which is best prevented by the sheathless application of balloon catheters [58].

As the patient's cardiac performance improves, the IABP support must be removed step by step. First of all, all inotropic medication should be lowered (dobutamine or dopamine dose $\leq 5 \mu\text{g/kg/min}$) parallel to hemodynamic stability, cardiac output, and mixed venous oxygen saturation changes. The next step to reduce balloon augmentation by one of two different methods: decreasing counterpulsation intervals or slow, step-wise deflation. Because a stagnation of the balloon catheter within the blood stream can cause microclots on its surface, decreasing of

augmentation levels seems more complication-free. Deflating the balloon catheter simultaneously decreases MCHS; a 50% reduction over 12 to 24 hours is a good indicator of successful weaning, terminating with the removal of the catheter.

5.2. Extraaortic counterpulsatile support (EACPS)

Extraaortic balloon pump (EABP), C-Pulse, is a new, counterpulsatile, nonblood-contacting device that involves placement of an inflatable cuff with a polyurethane balloon and polyester wrap around the ascending aorta for the management of end-stage HF patients, who remain symptomatic despite IABP therapy with optimum PHS [59]. C-Pulse is designed to provide permanent, long-term, continuous partial MCHS for end-stage HF patients [60]. The cuff inflates inwardly causing thumb-print deflection of the outer curvature of the ascending aorta, which creates a pressure across the aortic wall ranging from 6 to 25 mmHg. Approximately 20–30 mL of ascending aortic blood volume can be displaced per beat, depending on the cuff size and aortic diameter. The implantation is achieved via midline sternotomy, without cardiopulmonary bypass. There is no any deterioration in the aortic valve and aortic regurgitation, no intimal disruption and only minor thickening of the adventitia on microscopy [61].

5.3. Paraaortic counterpulsatile circulation support (PACPS)

Paraaortic blood pump (PABP) or *paraaortic circulatory device (PACD)* has been produced to enhance the hemodynamic effect and also to expand the indications of counterpulsation [62]. The first use in humans was disappointing, with large volume (100 mL) and on the ascending aorta implantation. Decreasing the device volume [63] and redesigning it so as to avoid the ascending aorta [64] were successful in decreasing initial systolic hypotensive symptoms and improving hemodynamic success, and for this reason it has been suggested that PABP may be more capable of efficiently supporting end-stage HF patients than IACPS or EACPS approaches. The IACPS systems should have limited dimensions and that is why IABP with limited capacity is preferred mostly in patients with moderate cardiac failure. However, IABP is unsatisfactory in patients with severe LVD, in whom systolic aortic pressure is lower than 70 mmHg. On the other hand, EACPS systems require a disease-free ascending aorta with appropriate length and therefore EABP can be used only in IABP-contraindicated patients with moderate cardiac failure because of nonblood contacting extravascular working principle. However, it needs a midline sternotomy incision and limited capacity related to the size of the ascending aorta could reduce device efficiency. If it is predicted that IABP or EABP may not provide enough stroke volume, blood pressure, and effective support in patients with moderate or more advanced LCOS (CMPs, myocarditis, etc.), PABP may provide better support. Additionally, PABP support must be preferred longer than a couple weeks in patients with severe LVF because it provides higher stroke volume, fewer vascular complications (ischemia, amputation, etc.), allows mobilization, and may be a better bridge to LVAD implantation or HTx [65]. There are several devices to provide PACP, but their usage is limited in special patient population or animal studies [66]. Partial unloading of the failed LV may interrupt the progressive hemodynamic deterioration of HF and improve quality of life in patients with earlier stages of HF. This partial support provided by PACDs may reduce native ventricular workload, augment myocardial blood flow, support positive myocardial remodeling, and prevent RVF [67, 68]. They do not require CBP support during implantation, and a major branch artery is

usually the preferred site for in- and outflow graft anastomosis. These devices preserve heart integrity, unload the LV, decrease its energy consumption, enhance native left ventricular functional performance, and retain pulsatility of flow. Recovery occurs usually within the first 3–6 months on mechanical assistance (bridge to recovery). The other philosophy about PACDs is to maintain arterial wall physiology with natural counterpulsatile flow.

6. Mechanical circulatory support (MCS)

End-stage HF is usually treated, healed, and stabilized by pharmacologic and/or mechanical hemodynamic support, but advanced HF is characterized by increasing frequency of intervals of decompensation, rehospitalization, and reintervention. If the MHS is insufficient for the recovery of LCOS, MCS is required to maintain CO (Table 11). Temporary MCS devices increase arterial blood circulation with or without extracorporeal oxygenation to provide an adequate CO, which acts as a parallel or serial artificial circulation to the physiologic circulation pattern. Permanent mechanical pumps provide a parallel artificial circulation of failed ventricles or entirely assume the pump function of the resected heart. Short-term devices are extracorporeal or paracorporeal pumps located outside the body, whereas durable devices are intracorporeal pumps implanted inside the body. The definitions of circulatory supports are dependent on cardiac chambers and oxygenation (Table 12).

	Counterpulsation	Short-term VAD	Long-term VAD
LVEF	<40%	<30%	<25%
LVD	No	Yes/no	Yes
Systolic ABP	<90 mmHg	<80 mmHg	<80 mmHg
Mean ABP	<60 mmHg	<50 mmHg	<50 mmHg
CVP	≥15 mmHg	≥18 mmHg	≥20 mmHg
Mean PCWP	≥15 mmHg	≥18 mmHg	≥20 mmHg
CI	≤2.2 L/min/m ²	≤2 L/min/m ²	≤1.8 L/min/m ²
SVR			>2100 Dynes/cm/sec
Inotropic agents with high doses	≤2	≥2	>2
IABP	No	Yes	Yes
Urine output	<0.5 mL/kg/h	<0.5 mL/kg/h	<20 mL/h
Metabolic asidosis	Yes/no	Yes/no	Yes
HRF	No	Yes/no	Yes/no
Application stage	First	Second	Second or last

ABP = arterial blood pressure; CI = cardiac index; CVP = central venous pressure; HRF = hepatorenal failure; IABP = intraaortic balloon pump; LVD = left ventricular dilatation; LVEF = left ventricular ejection fraction; MCS = mechanical circulatory support; PCWP = pulmonary capillary wedge pressure; SVR = systemic vascular resistance; VAD = ventricular assist device.

Table 11. Hemodynamic indication criteria for MCS in patients suffered heart failure.

Ventricular contribution: to decrease ventricular unloading and work index
<ul style="list-style-type: none"> • <i>Ventricular assist</i>: ventricular outloading through the left ventricular cavity directly (after mitral valve) • <i>Ventricular support</i>: ventricular unloading through the left atrium (before mitral valve)
Cardiac relinquishment: to circulate out-of-heart uni- or biventricularly
<ul style="list-style-type: none"> • <i>LV-bypass</i>: no-loading of the left ventricular • <i>RV-bypass</i>: no-loading of the right ventricle • <i>BV-bypass</i>: no-loading of both ventricles
With external oxygenator: to oxygenate blood in the external circulatory circuit
<ul style="list-style-type: none"> • <i>va-ECCPS</i>: veno-arterial circulatory assistance with external oxygenation • <i>va-a-ECCPS</i>: venoatrial-arterial circulatory assistance with external oxygenation • <i>aa-ECCPS</i>: atrio-arterial circulatory assistance with external oxygenation • <i>vp-ECCPS</i>: veno-pulmonary circulatory assistance with external oxygenation
BV = biventricular; ECCPS = extracorporeal cardiopulmonary support; LV = left ventricular; MCS = mechanical circulatory support; RV = right ventricular.

Table 12. Definitions of MCS in heart failure.

After full implementation of pharmacological and MHS therapies, most acute failed hearts after cardiogenic shock, interventional coronary revascularization, or surgical or percutaneous cardiac procedures can recover from LCOS within hours (peroperatively) or days (postoperatively). When this primary treatment strategy does not work or fails during a situation of intractable decompensated HF, MCS devices are the only life-saving instruments. These devices can be also used as a bridge to keep patients alive if weaning from CPB is not possible or when intractable LCOS does not recover. Consecutive or combined usage of these devices with or without extracorporeal oxygenation could be also an effective, maybe, an essential preference to get a successful outcome [69].

The working mechanism of MCS devices in HF syndrome is very simple: sucking circulatory blood under negative pressure and ejecting it into the systemic or pulmonary arterial circulation. The inflow cannula (temporary) or inlet tube (permanent) is inserted in the relevant ventricle and the outflow cannula (temporary) or outlet graft (permanent) is connected to the ventricle-associated main artery. These devices have two different action principles: pulsatile or continuous flow. Devices working by pulsatile flow have a blood-compatibility chamber and a moveable diaphragm separating the chamber into the blood and air spaces. The blood space is connected to the aorta or main pulmonary artery through a graft forced with a prosthetic valve. The air space is connected to a compressor-console providing power for counterpulsation through inflation and deflation. Devices working by nonpulsative flow have a blood-compatibility compartment and a frictionless turnable rotor directing input flow to the related circulation.

Pulsatility is the indispensable principle of the native, physiological, durable, regulated, and protective circulation in human. Pulsatile flow has several benefits for maintaining natural life (Table 13). The superiority of pulsatility over continuous flow has not yet been definitively

demonstrated, but several studies have addressed adverse nonphysiological transformation in the vascular bed, inequable neuroendocrine responses, and device-related complications from mechanical continuous circulation. More complicated extracorporeal devices are required to produce pulsatile flow, while pulsatile intracorporeal devices require more space than centrifugal pumps if used for uni- or biventricular support; however, only total artificial hearts produce the true pulsatile flow as prosthetic HTx.

There are two main types of extracorporeal pumps with different working mechanisms (**Table 14**). Pulsatile pumps are often used in biventricular failure and in pediatric patients [70]. Nonpulsatile pumps are mostly preferred for CPB and MCS. Roller pumps, which generate forward blood flow by roller compression, rate of rotation, and the length of the compression raceway, are useful for

-
- Transmission of energy to the microcirculation
 - Reduction critical capillary closing pressure
 - Augmentation of lymphatic flow
 - Improvement of tissue perfusion
 - Amelioration of cellular metabolism
 - Alleviation of vasoconstrictive reflexes
 - Diminution of acidosis
 - Regulation of neuroendocrine responses
-

Table 13. Physiologic effects of pulsatile flow.

-
- | | |
|------|--|
| (I) | Pulsatile flow pumps |
| | 1. Abiomed |
| | 2. Thoratec paracorporeal ventricular assist device |
| | 3. Excor |
| (II) | Nonpulsatile flow pumps |
| | 1. Roller pumps |
| | 2. Centrifugal pumps |
| | a. Medtronic Bio-Medicus |
| | b. Maque Rotaflow |
| | c. Levitronix CentriMag |
| | d. TandemHeart |
| | 3. Axial pumps |
| | a. Impella |
-

MCS = mechanical circulatory support.

Table 14. Devices for temporary MCS.

CPB during open heart surgery, but not for circulatory support due to hemolysis and tubing wear. Extracorporeal continuous flow pumps are useful for CBP as well as extended t-MCS with fewer adverse effects than roller pumps. Intracorporeal devices are designed with a smaller structure using two separate pump mechanisms: axial flow pumps have a pump rotor parallel to the blood path, and centrifugal pumps have an impeller rotor perpendicular to the blood path. The rotor is magnetically levitated, and rotation is achieved without friction or wear, thus minimizing blood trauma, mechanical failure, and heat generation. These devices work by an external motor-driven system, direct-drive system, or self-bearing system. In direct-drive system, the impeller becomes the motor rotor supported by a separate levitation system. In self-bearing system, both the drive and the levitation coils share the same stator core [71].

Because the duration of their usage could be limited, the decision for the destination goal should take into hemodynamic, hematologic, and neurologic courses. Even though the gold standard therapy for end-stage HF is HTx, this is possible in only a small number of patients due to limited organ availability. These devices are generally used to maintain adequate organ perfusion for several days, but more time could be required before a final decision is made (**Table 15**). Bridging to curative treatments should be life-saving and any device could be effective, but do not hesitate to change the treatment stages and devices.

Designed to assist the native heart, MCS devices are differentiated by the implant duration [short-term (<10 days), mid-term (10–90 days), long-term (>90 days)], indication [temporary (bridge therapy) versus permanent (destination therapy)], type (cardiopulmonary versus circulatory), approach (percutaneous versus surgical), location (extracorporeal versus intracorporeal), flow characteristic [pulsatile versus continuous], pump mechanism (volume displacement, axial, centrifugal), and the ventricle(s) supported (left, right, biventricular) [72].

6.1. Temporary mechanical cardiorespiratory support (t-MCRS)

Acute decompensation of cardiac functions requires emergent circulatory support when pharmacological treatment and/or counterpulsatile support are ineffective or when weaning from CPB fails (**Table 16**). There are several options for t-MCS, which can be applied percutaneously or centrally, but right ventricular and respiratory functions are decision-making factors [73]. Sufficient oxygenation by the lungs suspends usage of external oxygenator, but associated RVF necessitates its usage. Temporary cardiorespiratory support (t-MCRS) devices are designed to rapidly reestablish adequate organ perfusion and oxygenation. Biventricular t-MCRS is the most common approach to maintain adequate CO and oxygenation in the presence of severe RVF; however, univentricular t-MCRS can be the preferred approach in the absence of significant RVF. An ideal device should support adequate flow, maximal hemodynamics, sufficient oxygenation, and avoid need for anticoagulation with its serious related serious complications (**Table 17**). After echocardiography fails to reveal a surgically correctable cause, a temporary mechanical device is considered for MCS according to several hemodynamic data (**Table 11**). Daily follow-up with transthoracic and/or transesophageal echocardiography is mandatory to evaluate biventricular function, regional wall motion abnormalities, valvular mechanics, septal malformations, and extracardiac compression, as well as native heart recovery. On the other hand, the stabilized patient should also undergo daily evaluation for end-organ functions, hematologic and infectious conditions, and neurologic status.

Bridge to recovery (BTR): *Salvage therapy.* Clinical situation consists of either acute developed cardiogenic shock or acutely decompensated Stage-D HF. Acute huge myocardial infarction with or without mechanical complications, acute myocarditis, and postcardiotomy syndrome after cardiac surgery cause acutely developed myocardial dysfunction, which can be refractory to optimal treatment via PHS and counterpulsatile MHS despite viable myocardium. Any reason can worsen and decrease stable Stage-D HF into unstable condition with severe LCOS. The myocardium could be recovered by MCS devices via unloading the left ventricular in a couple of hours or days (<4–7 days), and after that patients should be put into advanced bridging therapies. Daily echocardiographic examinations are guiding and following practices to investigate the reverse remodelling of the failed myocardium. During this period, the main goal is to keep patients alive.

Bridge to decision (BTD): *Rescue therapy.* Acutely cardiac failure subsequent to myocardial infarction or cardiac operations, or acutely decompensation of Stage-D HF requires optimal treatment via MHS and/or MCS devices (1) to keep patients alive, and then (2) to maintain vital functions due to mechanical supported cardiac output, and finally (3) to gain time for decision to the most appropriate curative or egress treatment solution for related patients. Clinicians have a couple of days (<14 days), but not more than one week, to evaluate each patient separately with his/her own cardiac pathology and to decide the next step(s). During this period, the main goal is to let the heart in rest and no-load, and also to keep extracardiac organs in normal functions.

Bridge to wean (BTW): *Separation therapy.* Improvement in cardiac functions and healing of acute decompensation of acute or chronic HF improves patient’s status and makes it possible to disconnect mechanical devices. After the hemodynamics recover completely in several days or weeks (<30 days), weaning protocol is started via reducing all pharmacological agents to their minimum dosages, improving respiratory functions, and decreasing mechanical support levels. Patients should be followed with daily echocardiography and pulmonary arterial catheterization (wedge pressure, mixt venous oxygen saturation). During this period, the main goal is to keep patients noncardiacly complication-free.

Bridge to curative surgical and/or percutaneous interventions (BTI): *Supportive therapy.* Associated curable cardiac pathologies (CAD, MR, postinfarct VSD, etc.) could be treated to improve cardiac functions and to prevent new decompensations. The hemodynamically stable condition gained by MCS devices enables clinicians (1) to revascularize ischemic myocardium, (2) to repair these structural mechanical complications, (3) to rescue the acute failed heart, (4) to recovery myocardial dysfunction, and (5) to bridge to weaning or advanced treatments. During this period, the main goal is to keep extracardiac organs in normal functions, and also to provide hemodynamic with or without respiratorial support during procedures.

Bridge to bridge (BTB): *Exchange therapy.* Short-term mechanical supportive devices cannot provide adequate flow and facilitate further improvement in the clinical status of patients, as the result patients cannot be weaned from MCS. The preferred MCS type should be switched more a failed-oriented type of MCS or more durable approach. Weaning from right ventricular and/or pulmonary support make it possible to disconnected venous cannulas or oxygenator from the circuit (bridge from va-a-ECCPS to aa-ECCS).

Bridge to candidacy (BTC): *Preparatory therapy.* Switching from t-MCS to p-MCS due to the necessity of the long-term follow for successful recovery is necessity for the decision (1) to wean from the device, (2) to use the device as the destination therapy, or (3) to take the patients into the transplantation list. The reversibility of the elevated PVR or the prolonged healing of damaged myocardium requires a prolonged treatment-period (>30 days), usually a couple of months, but not more than six months. Long-term predicted recovery should be verified by invasive tests a significant reduction in PVR. During this period, the main goal is to keep patients in their daily lives.

Bridge to destination (BTD): *Continuity therapy.* Long-term mechanical support is a durable treatment alternative to HTx in with Stage-D HF patients, who are not eligible for transplantation due to extracardiac diseases, irreversible elevated PVR, advanced age, or donor inability. Left ventricular assist devices may prolong and improve the quality of life.

Bridge to transplantation (BTT): *Curative therapy.* Irreversible myocardial function is the main indication for HTx in the decompensated or device-dependent Stage-D HF. Progressive lengthening of waiting times on transplantation lists can be an indication for LVAD implantation, but this reason is most pertinent to bridge to destination therapy. On the other hand, there is no widely accepted guideline to show the indication and timing for a mechanical supportive device placement as a bridge treatment. The true indications for this therapy are (1) patients with implanted p-MCS devices with/without complications, (2) unrecoverable patients supported with t-MCS devices, and (3) borderline patients on the bridge to candidacy protocol.

Table 15. Bridging from live-saving t-MCS to advanced therapy modalities.

Acute myocarditis
Acute huge myocardial infarction with/without mechanical complications
Cardiogenic shock
Cardiopulmonary arrest
Postcardiotomy syndrome
Acutely decompensation of Stage-D heart failure
Intractable decompensation of end-stage cardiomyopathies
Intractable ventricular tachycardia in end-stage cardiomyopathies
Bridge to destination therapy or heart transplantation
Postimplant right ventricular failure

Table 16. Indications of t-MCS for heart failure.

Decrease preload
Decrease pulmonary capillary wedge pressure
Not increase afterload
Augment cardiac output
Increase coronary perfusion
Improve peripheral tissue perfusion
Provide adequate oxygen delivery

Table 17. The primary hemodynamic goals of t-MCS.

6.1.1. Cardiopulmonary bypass (CPB)

The first used life-supportive approach is CBP with a roller or centrifugal pump for circulatory assistance and an oxygenator for respiratory reinforcement during open heart surgery. This shortest extracorporeal circulation has several parts resulting in hemolysis, especially the cardiotomy suction and venous reservoir. Failing to wean from bypass after cardiac procedures enforces to prolong circulatory support via CPB. Because this approach is not suitable for short-term or longer circulatory support, CPB has been used only for ultrashort-term (<1 day) circulatory assistance. The main differences of CBP circuit are the drainage of venous blood, typically by gravity, into venous reservoir of the heart-lung machine, and aspiration of blood from the surgical field into the reservoir. Both of these can cause also inflammatory and humoral responses, thrombosis and bleeding problems. The rest of the supportive mechanism is similar with the other t-MCPS devices: to pump venous blood through an oxygenator for gas exchange, and therefrom into the arterial circulation. This basic extracorporeal perfusion system can be used for partial or total circulatory and respiratory support, or partial support of the LV. Modern membrane oxygenators add up to 470 mL of O₂ and remove up to 350 mL of CO₂ per minute at

1–7 L of flow with resistances of 12–15 mmHg per liter blood flow. Preferable pumps are centrifugal ones consisting of a vaned impeller or nested smooth plastic cones, which propel blood by centrifugal force when they rotate rapidly. Centrifugal pumps produce forward pressure of up to 900 mmHg, but only half as much of negative pressure, and therefore, less cavitation and fewer gaseous microemboli. Flow rate should be set to maintain mean arterial pressure at ≥ 70 mmHg at 35 to 37°C, with a hematocrit of 30%. This flow rate provides and maintains adequate body perfusion, with higher mixed venous oxygen saturation $>60\%$.

It is meaningful to use CBP as a mechanical support only in the theater for *ultrashort-term* (*several hours*) assistance, but advanced technology provides more appropriate devices for short- and long-term MCPS. There are several side effects of CBP that preclude its usage as a short- and long-term cardiopulmonary support. The main problem is left ventricular distention and lack of unloading during CPB support, which will be prevented by insertion of a vent catheter into the LA or LV. The second limitation is the necessity of full dose heparinization to gain an activated clotting time greater than 400 seconds during extracorporeal circulation to prevent thrombo-embolic events, which usually causes bleeding problems. The third possible hazard is massive air embolism due to the integrity of the extracorporeal circuit. The fourth side effect is generalized inflammatory reactions, which result in a number of undesired pathophysiologic cascades. The fifth negative damage is possible lung injury, which is inevitable during CPB support due to increased pulmonary capillary permeability, interstitial lung water, and adverse inflammatory responses.

6.1.2. Extracorporeal life or cardiopulmonary support (ECLS or ECCPS)

The casually accepted term for these support strategies is ECMO, but the true definition must be extracorporeal cardiopulmonary support (ECCPS) while using for treatment in decompensated Stage-D HF or extracorporeal life support (ECLS) while using for similar support in acute cardiogenic shock. Although the unsuitability of CBP for short- or long-term ECLS has been established, its principles have been applied to never small, durable, practical, integrated, and mobile devices that are practical for providing ECLS in all appropriate circumstances. The principal aim of ECLS is to provide acute temporary ECCPS globally as a bridge to more durable therapy in patients with cardiorespiratory failure refracted to maximal conventional therapy [74]. For extracorporeal membrane oxygenation (ECMO), an oxygenator is inserted in the extracorporeal circuit for gas exchange before returning patient's venous blood to the patient's arterial circulation, which is driven by a centrifugal pump. They are suitable for t-MCS, but single or multiple replacement of the failed oxygenator with a new one can allow prolongation of ECCPS to more than 1 month if myocardial recovery is the desired and expected goal. If pulmonary functions are well or pulmonary recovery occurs during ECCPS, the external oxygenator is not necessary and it must be disconnected from the circuit to provide acute or prolonged temporary extracorporeal circulatory support (ECCS) for the LHF or RHF. Double established ECCSs could be used separately for biventricular HF patients with unimpaired respiratory functions.

The devices designed for short-term ECCPS have a number of advantages in comparison with CPB (lower dose of heparin, a continuous circuit, etc.). A hollow-fiber membrane oxygenator

with an integrated heat-exchange system operated by a centrifugal pump provides circulatory, respiratory, and thermatory supports. These pumps are totally nonocclusive and afterload-dependent, and when myocardial recovery occurs, physiological circulation overtakes artificial circulation, manifesting as reduced device flow. These pumps do not create excessive output pressure (so as not to rupture the circuit) or significant negative input pressure (so as to avoid cavitation and microembolus). Using this system, ECCPS flow is maintained between 4 and 6 L/min by providing a pump speed of between 3000 and 3500 rpm, with higher pump speed risking mechanical trauma to blood cells. The heat exchanger provides normothermia during ECCPS, which is mandatory for physiologic body functions. A biocompatible heparin-coated bypass circuit provides an antithrombotic surface to reduce or eliminate the necessary dose of heparin and inflammatory responses. Because roller pumps cause hemolysis beyond 4 and 5 hours of usage, continuous flow pumps are preferred for ECCPS.

The real problem with ECCPS in end-stage HF patients is how to protect and unload one or both ventricles. Conventional ECLS bypasses both ventricles through the venous drainage and arterial inflow, and physiologically, that will unload the RV without unloading the LV due to the increased afterload. In the borderline depressed LV or during the recovering process of LVF, both a remarkable drop in preload and a certain rise in afterload reduce left ventricular wall stress, produce smaller LVEDV, augment coronary perfusion, and ultimately improve left ventricular contractility. However, if the heart is dilated and/or contracting poorly, a markedly increased afterload handicaps any offset in both LVEDV and LVESV by blocking the opening of the aortic valve. Theoretically, left ventricular wall stress and myocardial oxygen consumption remain increased and inhibit the recovery of the failed LV. The first goal should therefore be to unload the LV using IABP and/or left atrial venting. The second target is to deliver the highly oxygenated blood directly to the coronary and cerebral circulations. Adding an IABP device to support left ventricular systolic function (by reducing afterload) and coronary perfusion (by increasing aortic diastolic pressure) is an integral part of ECLS therapy. Although ECLS balances hemodynamics, the insertion of IABP aggrandizes coronary and cerebral perfusion effects and also maintains aortic valve opening more effectively.

Establishment of ECCPS could be central or peripheral: central approach is superior due to better left ventricular unloading and the avoidance of peripheral vascular complications; however, peripheral cannulation permits later decannulation without reopening the chest. Both approaches are effective for managing cardiorespiratory failure with uni- or biventricular dysfunction associated with respiratory dysfunction (**Table 18**).

Central ECCPS is established through cardiac cannulation and is usually preferred for the failure of weaning from the bypass in the theater or postcardiotomy syndrome that develops in the ICU. The preference of central cannulation is based on several physiological hemodynamic requirements that allow shorter myocardial recovery for the acutely decompensated heart: effective biventricular unloading, highly adequate blood flow, sufficient tissue oxygenation, and easy transition from the cardiopulmonary support to left ventricular circulatory support. This approach is superior to peripheral ECCPS due to better coronary, cerebral, and upper extremities perfusion and easy insertion of left atrial vent. Central ECCPS is established via central cannulations used during cardiac surgery for postcardiotomy syndrome, or via full

ECLS- strategy	Bypass	Type	Establishment between	Approach
A. ECCPS (with ECMO)				
va – ECCPS	bv-bypass	veno-aortic veno-arterial	RA – Ao femoral and/or jugular vein – femoral or subclavian artery	Median sternotomy Peripheral percutaneous
va-a-ECCPS	bv-bypass	biatria-aortic venoatrio-aortic venoatrio-arterial	(RA + LA) – Ao (femoral vein + LA) – Ao (femoral vein + LA) – femoral or subclavian artery	Median sternotomy Median sternotomy Peripheral percutaneous
aa – ECCPS	lv-bypass	atrio-aortic atrio-arterial	LA – Ao LA – femoral/subclavian artery	Median sternotomy Peripheral percutaneous
vp – ECCPS	rv-bypass	atrio-pulmonaric venopulmonaic	RA – PA femoral and/or jugular vein – PA	Median sternotomy Peripheral percutaneous
B. ECCS (without ECMO)				
lv – ECCS	lv-bypass	atrio- or ventriculo-aortic atrio- or ventriculo-arterial	LA – or LV – Ao LA – or LV – femoral or subclavian artery	Median sternotomy Mini-thoracotomy
rv– ECCS	rv-bypass	atrio-pulmonaric veno-pulmonaric	RA – PA femoral and/or jugular vein – PA	Median sternotomy Mini-thoracotomy
bv– ECCS	bv-bypass	separately lv- and rv-ECCS		

ECCPS = extracorporeal cardiopulmonary support; ECCS = extracorporeal circulatory support; ECLS = extracorporeal life support; ECMO = extracorporeal membranous oxygenation; bv = biventricular; lv = left ventricular; rv = right ventricular; Ao = aorta; LA = left atrium; LV = left ventricle; PA = pulmonary artery; RA = right atrium.

Table 18. Temporary ECLS strategies for end-stage HF patients.

or limited sternotomy incision (reverse-T upper hemisternotomy). Both cannulas are taken out from the mediastinum below the xiphoid or through the jugulum. A new design of a biventricular assistance circuit including an oxygenator-bypass line (Kiralı circuit) assists and provides the improvement of life-saving HF therapy from the sophisticated immovable t-MCPS circuit to the simplest mobile t-MCS circuit (va-a-ECCPS).

Peripheral ECCPS is established through peripheric cannulation and usually preferred as a rescue approach in nonsurgical patients suffered from acute cardiogenic shock or decompensated HF. Any perfusion strategy creating a right to left shunt requires an oxygenator in the circuit. Peripheral ECCPS is generated through the femoral artery (peripheral or upstream) or the axillary artery (periphero-central or downstream). Femoral access is more commonly used in patients requiring urgent ECLS due to rapidity of insertion and avoidance of sternotomy. The most important drawback is the left ventricular afterload mismatch and inadequate left ventricular decompression, which will cause pulmonary edema in patients with very low native CO and severe MR. To assist left ventricular unloading, IABP is used concomitantly to reduce afterload and facilitate aortic valve opening. Failure of aortic valve opening may provoke catastrophic results such as intracardiac thrombosis with or without clot embolism, worsening of LVF, coronary malperfusion, and pulmonary edema. Several percutaneous alternative approaches can be used to unload the LV during peripheral ECCPS: transaortic left ventricular unloading, transseptal left atrial

decompression, atrial septostomy, and transapical left ventricular drainage. On the other hand, coronary and upper body hypoxia can occur if myocardial recovery occurs and lung function remains poor, or as mostly seen, if pump flow is reduced. Peripheral cannulation depends on the arterial structure and size, the presence of any occlusive pathology, and deficiencies in distal perfusion. A distal perfusion cannula is inserted in the selected artery distal to the inflow cannula and connected to the inflow cannula to perfuse distally to prevent extremities from ischemic complications. The same problem may develop in venous system, and a small cannula inserted into distal vein is connected into the outflow cannula to facilitate distal drainage.

Extracorporeal cardiopulmonary support is achieved using an ECMO system as described above. They can be designed according to uni- or biventricular support, and also the system must be prepared for weaning from biventricular and respiratory support step by step (Figure 3).

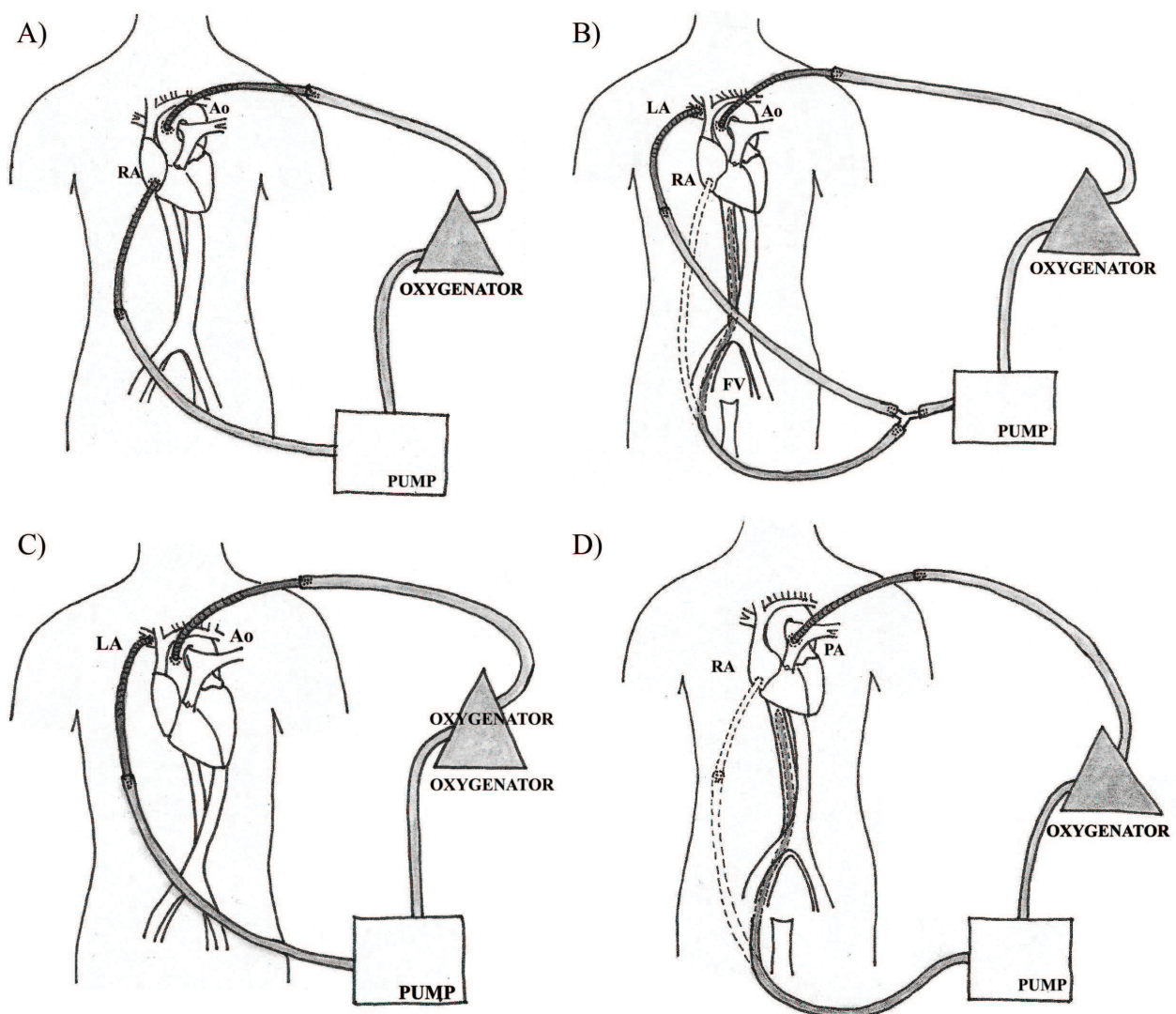


Figure 3. ECLS alternatives in Stage-D heart failure treatment. (A) va-ECLS (venoarterial ECMO). (B) va-a-ECLS (venoatrio-arterial ECMO). (C) aa-ECLS (atrio-arterial ECMO). (D) vv-ECLS (veno-venous ECMO). Ao = aorta; FV = femoral vein; LA= left atrium; RA = right atrium.

The ECCPS system can be created with several ways for different indications (**Table 18**).

va-ECCPS (va-ECMO) (biventricular bypass circuit) is the conventional ECMO system with biventricular bypass circuit by which a centrifugal pump drives blood from the patient's venous circulation through an externalized membrane oxygenator for gas exchange before returning the blood to the patient's arterial circulation. This approach is usually implemented percutaneously at the bedside in all emergent situations, in order to rescue patients suffering from fatal cardiac failure; however, a final decision about the most beneficial durable strategy should be made within a couple days (<7 days). If weaning does not seem possible, it is more appropriate to convert patients to a longer sustainable ECCPS circuit or to switch to an ECCS design.

va-a-ECCPS (va-a-ECMO) (biventricular unloading circuit; Kirali circuit) is a new format of a biventricular assistance circuit including biatrial drainage cannulas and an oxygenator-bypass line (Kirali circuit) assists and provides the improvement of life-saving HF therapy from the sophisticated immovable t-MCPS circuit to the simplest mobile t-MCS circuit (**Figure 4**); particularly it is meaningful in patients with expected RV and respiratory recovery in a couple of weeks (<1 month). This biventricular unloading circuit includes a centrifugal pump that drives blood from the patient's both atria through an externalized membrane oxygenator for gas exchange before returning to the patient's arterial circulation. This circuit has two venous cannulas: the first venous cannula (a multistage venous ECMO 28F cannula) is inserted percutaneously into the femoral vein or directly into the RA for venous drainage, and the second venous cannula (a malleable one-stage venous cannula ranged between 22F and 28F) is placed into the LA at first for left heart venting (drainage), and then for left heart bypassing (unloading). An arterial cannula (an arterial ECMO cannula ranged between 15F and 19F) is inserted into the distal ascending aorta or aortic arch, and the distal end of the cannula is placed distal to cerebral branches. Both left heart cannulas with or without the RA cannula are taken out below the sternal incision and the sternum is closed to prevent bleeding and to allow mobilization. Each outflow line has its own tap that allows blood sampling to follow blood gas and pulmonary recovery, and can be controlled by partial or total clamping to manage adequate blood drainage from each atrium according to the related ventricular dysfunction/recovery cascade. Peripheral venous cannulation is preferred for periods of brief support (<1 week) because decannulation of the percutaneously inserted femoral venous cannula is simple. If RV recovery is expected to take more than a week, then right atrial venous cannulation should be performed centrally or a small drainage cannula is inserted distal to the outflow cannula at the femoral vein to prevent peripheral venous complications. Daily echocardiographic examination introduces RV recovery, and frequently follow-up blood samples from the left atrial inflow line propound the pulmonary recovery. Weaning from the external oxygenator should be completed in ≥ 4 days, and the external oxygenator should remain in the circuit for the purpose of emergent actuation in case of unexpected respiratory failure during this weaning period.

Weaning from va-a-ECCPS protocol in end-stage HF patients is simpler than others and does not require reopening of the sternum or establish a new circuit and disconnection steps should be made long enough to observe any pulmonary complications or recurrence of respiratory failure (**Table 19**). Decannulation of peripheric venous cannula is very simple when RV

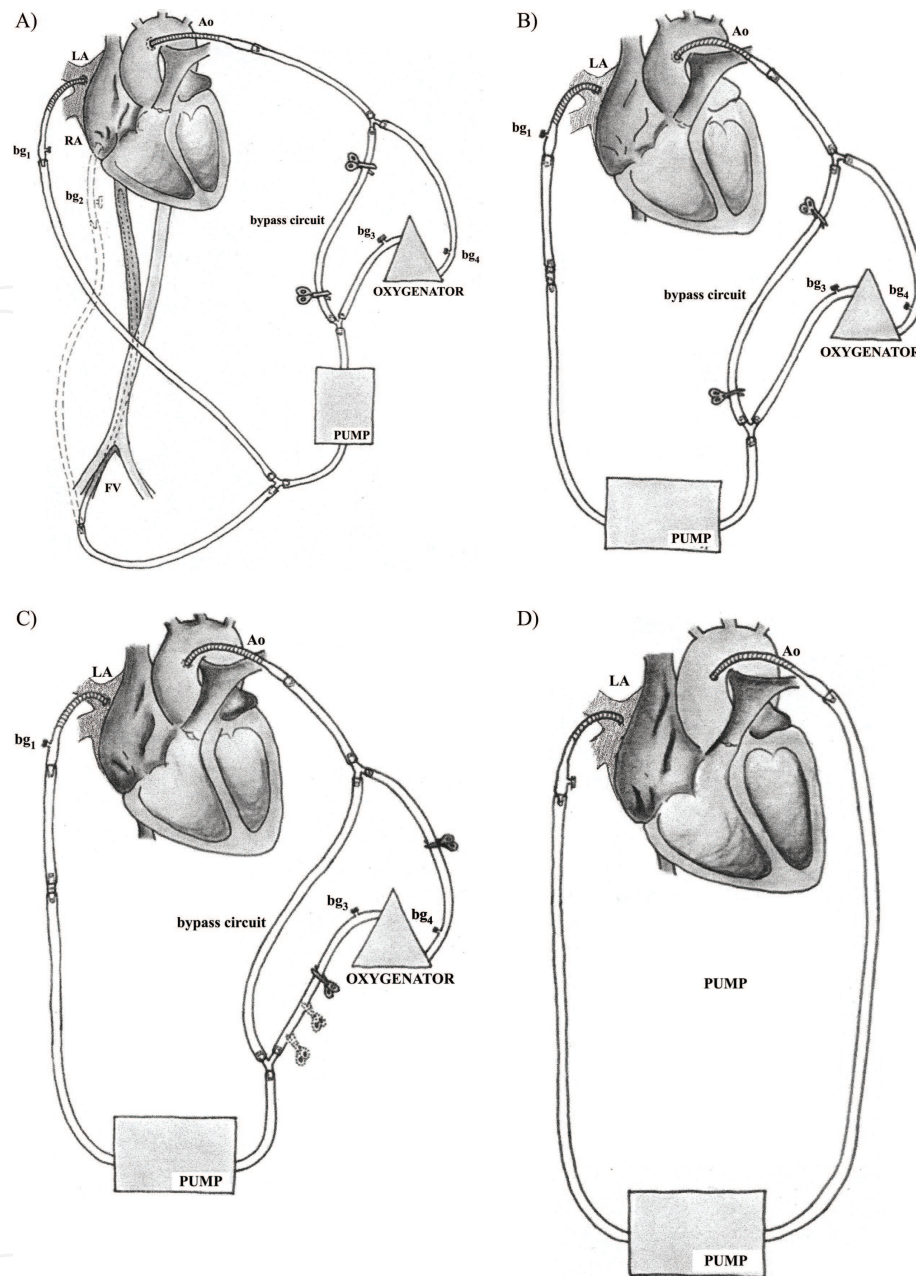


Figure 4. Venoatrial-arterial ECLS support (Kiralı Circuit for biventricular unloading). (A) The circuit is constituted between both atria and the arterial circulation for right heart, pulmonary, and left heart bypass. Left ventricular unloading is necessary for left heart bypass, right ventricular unloading is necessary for right heart bypass and as well as pulmonary bypass. Blood samples from bg₁ (pulmonary gas exchanges) and bg₂ (mixt venous) show oxygen saturations in patients, and bg₃ (preoxygenator) and bg₄ (postoxygenerator) gas exchanges; whereas arterial blood sample shows true body oxygenation. (B) After right heart recovery, right heart bypass line is removed from the circuit to get pulmonary and left heart bypass. (C) After pulmonary recovery, oxygenator bypass circuit is actuated to decrease oxygenator support. (D) After pulmonary recovery, oxygenator is removed from the circuit to get isolated left heart bypass. Ao = aorta; bg = blood gas sample; FV = femoral vein; LA= left atrium; RA = right atrium.

recovery is completed, and at this first stage, the circuit is converted to left heart bypass system supported with external oxygenator after removing right ventricular support (aa-ECCPS). After pulmonary recovery, the oxygenator could be removed from the circuit. First, the

First step	To convert va-a-ECCPS to aa-ECCPS after sufficiently recovery of the RV.
Second step	To reduce the oxygen delivery by respirator (res-FiO ₂) till 35–40%, while the oxygen delivery by external oxygenator (oxy-FiO ₂) is stabilized at 40%.
Third step	To open the oxygenator bypass line and to direct the left atrial blood flow through both oxygenator inflow lines nonocclusively with a flow ratio 3:1 (bypass line/on line) depending on membrane resistance, after blood samples from the left atrial cannula show effective native pulmonary oxygenation (left atrial oxygen saturation >95%) at least one day.
Fourth step	To reduce oxy-FiO ₂ until the air ratio (21%) or disconnect the external oxygenator from oxygen gas supply, after patient's oxygenation does not collapse at least one day.
Fifth step	To begin weaning from mechanical ventilation and to extubate the patient, after arterial oxygen saturation is maintained at a level higher than 95% with res-FiO ₂ 40% at least one day.
Sixth step	To disconnect the external oxygenator from the circuit and to switch aa-ECCPS to aa-ECCS, after arterial oxygenation does not retrogress after extubation at least one day.

Table 19. Disconnection steps from the external oxygenator.

oxygenator bypass line is taken over pump flow step by step, and the full declamping of this line allows approximately three times more blood flow than those passing through the oxygenator due to resistance of membrane. This strategy reduces oxygenator support and enables native lungs to oxygenate most part of the pump blood flow. Finally, oxygenator is switched off and disconnected, and at this stage, the circuit is converted to left heart bypass system without oxygenator (aa-ECCS). The last stage and the simplest LV-ECCS system allows patients to be discharged from the ICU and mobilized at the ward, and provides hemodynamically stable bridging to destination therapies (LVAD or HTx).

This stage of cardiopulmonary circuit used for ECCPS provides several benefits (**Table 20**). This new strategy is independent of recovery durations, and unless any fatal complication occurs, the supportive therapy can be extended for weeks until a destination treatment could be performed, because it is easier to exchange failed oxygenator and/or pump head with a new one in this strategy, converting from “ECCPS to ECCS” or reverse, and from “va-a to aa” or reverse. The presence of the functionally significant MR facilitates left ventricular unloading through the left atrial cannula, but it can increase pulmonary congestion if the pump flow is not increased to sustain and maintain PCWP < 18 mmHg and CVP < 12 mmHg. In this circumstance, wean protocol from LV-ECCS should be started after mitral valve recovery or any percutaneous or transapical mitral valve repair intervention. The presence of the competent mitral valve, which does not facilitate left ventricular unloading due to blocking regurgitant flow, and the increased afterload, which does not enable left ventricular ejection, impair LV recovery. The best solution is provided by arterial pulsation augmenting LV unload via aortic valve opening during all left heart bypass steps.

aa-ECCPS (aa-ECMO) (left ventricular bypass circuit) is a univentricular ECMO system in which the left heart bypass circuit uses a centrifugal pump to drive blood from the LA through an external membrane oxygenator for gas exchange before returning to the patient's arterial circulation. This approach is preferred in patients with LVF and respiratorial insufficiency without RVE, who could not be managed with full mechanical ventilation, or can be a part of va-a-ECCPS.

Stage	Bridging	Established	Converting to	Benefits
Initial	Bridge to recovery	t-MCS MRS	va-a-ECCPS MRS	Effectively providing of biventricular support and gas exchange through a single pump configuration; Decompression of the left heart, reducing the LV wall stress, better coronary and body perfusion, minimizing oxygen consumption
First	Bridge to RV recovery	va-a-ECCPS MRS	aa-ECCPS MRS	Decreasing PAP, PCWP, RV afterload; Improvement of the RV; Disconnection of RV support
Second	Bridge to pulmonary recovery	aa-ECCPS MRS	aa-ECCS MRS	Decreasing LAP, pulmonary unloading; Improvement of gas exchange and adequate oxygenation; Facilitating of pulmonary recovery; disconnection oxygenator
Third	Bridge to decision	aa-ECCS MRS	aa-ECCS spontaneous ventilation	Significantly decreasing of LVEDV and LVEDP; extubation
Fourth	Bridge to bridge	aa-ECCS	aa-ECCS	Possibility of weaning, listing for HTx, or candidate for durable therapy; Mobilization in ICU
Fifth	Bridge to candidacy	aa-ECCS	wean or p-MCS	Mobilization at ward
Sixth	Bridge to destination therapy	aa-ECCS	LVAD or HTx	Destination treatment

aa = atrio-aortic; ECCPS = extracorporeal cardiorespiratory support; ECCS = extracorporeal circulatory support; HTx = heart transplantation; ICU = intensive care unit; LAP = left atrial pressure; LV = left ventricular; LVAD = left ventricular assist device; LVEDP = left ventricular end-diastolic pressure; LVEDV = left ventricular end-diastolic volume; p-MCS= permanent mechanical circulatory support; t-MCS = temporary mechanical circulatory support; MRS = mechanical respiratory support; PAP = pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; RV = right ventricular; va-a = venoatrio-aortic.

Table 20. Bridging effects of va-a-ECCPS in Stage-D HF patients.

vp-ECCPS (vp-ECMO) (right ventricular bypass circuit) is a univentricular ECMO system in which the right heart bypass circuit uses a centrifugal pump to drive blood from the patient's vena cava or the RA through an external membrane oxygenator for gas exchange before returning to the patient's pulmonary circulation. This approach is preferred in patients with RVF and respiratorial insufficiency without LVEF, who could not be managed with full mechanical ventilation. The more preferred indication can be postimplant RVF accompanied by respiratory failure.

6.2. Temporary mechanical circulatory support (t-MCS)

Most patients requiring MCS are candidates for t-MCRS, but there are some conditions that do not require ECMO support. Patients whose pulmonary function is sufficient with spontaneous or mechanical ventilation may be able to avoid or wean from oxygenator use during MCS for decompensated HF. Patients with isolated univentricular failure can mostly be treated with counterpulsatile devices, but if hemodynamic parameters do not improve more aggressively t-MCS should be performed using an ECCS system to assist the failed ventricle. Another alternative is intracorporeal circulation support (ICCS), which can be preferred in cases of cardiogenic shock or left ventricular unloading during va-ECCPS.

6.2.1. Extracorporeal circulation support (ECCS)

Isolated left or right heart ECCS is provided by a centrifugal pump; however, an external oxygenator may be implanted in the circuit if any acute respiratory decompensation develops (switch from ECCS to ECCPS). The ECCS is mostly preferred in decompensated CMPs with LVF or refracted LVD to keep patients alive until destination treatments. Another indication for weaning patients from ECCPS-based t-MCPS to ECCS-based t-MCS, by removing the oxygenator from the circuit in patients suffering from acute severe postcardiotomy syndrome. In both situations, moribund patients should be treated and followed very carefully, and HTx should not be considered unless the patients show significant recovery from multisystem organ failure. The ECCS system can be used many weeks to improve clinical status of patients. Limited recovery with appropriate t-MCS could encourage surgeons to implant more permanent LVADs to eliminate external lines and pumps, but t-MCS is also an acceptable treatment modality to maximize patient survival, for mobilize patients, to provide better rehabilitation, and to prepare them for transplantation. Temporary ECCS can be created surgically central for LV support or percutaneously peripheral for RV support (**Table 18**).

aa-ECCS or left-to-left ECCS (left heart bypass system) between the LA and aorta (or arterial circulation) is the preferable approach to sustain the end-stage HF patients with irreversible LVF, but preserved right ventricular and pulmonary function. Any of the several types of centrifugal pumps is chosen for long-term left ventricular ECCS (for several weeks), because all of them have similar technologic principles. The inflow cannula is connected to the pump, and the outflow cannula is inserted into the arterial circulation. The inflow cannula is usually inserted in the LA. Left atrial insertion of a malleable venous cannula ranging from 22 to 28F is performed through the left atrial wall just at the interatrial groove, not on the right pulmonary veins like as in left atrial vent insertion, because the drainage cannula is big enough to injury the walls of the pulmonary vein. Similar to standard mitral valve surgery, a limited Sondergaard's plane is dissected approximately 2 cm from the junction of both right pulmonary veins at the left atrial wall. Then, two pledgeted sutures are used to fix the cannula and prevent bleeding. After the removal of the cannula, the dissected tissues support the sutures like a pillow to block bleeding. Left ventricular cannulation is not commonly chosen when the LV is not dilated in postcardiotomy syndrome, or when the left ventricular apex is to be left untouched for permanent LVAD implantation. Two pure-string sutures are placed on the apex, and after the apex is incised. Tubbs dilators are used to enlarge the vent hole for the venous cannula, and finally the cannula is secured with purse-string sutures. The outflow cannula is inserted into the distal ascending aorta or aortic arch, and a longer ECMO arterial cannula ranging from 15 to 19F is placed. The distal edge of the cannula locates distal to the cerebral arteries in order to avoid cerebral embolic complications. This system is preload-dependent, with an ideal PCWP maintained between 18 and 20 mmHg and CVP between 8 and 12 mmHg, and they should be monitored. Lower dose heparin infusion is necessary (ACT < 200 seconds) to prevent any thromboembolic complication. Absolute contraindications are aortic insufficiency that is any more than mild in degree, or intracardiac septal defects.

vp-ECCS or right-to-right ECCS (right heart bypass system) between the RA (or vena cava through the femoral vein) and pulmonary artery is rarely a preferred approach for isolated RVF

because the normally functioning LV can take on most of the right ventricular work. The main indication of right heart bypass systems is acute postimplant RVF after LVAD implantation. Permanent LVADs are increasingly used worldwide, and the most commonly observed cardiac complication is RVF after implantation [75]. Therefore, special attention should be devoted to the evaluation of the right ventricular function when patients are assessed for LVAD implantation. The outflow cannula is inserted either into the RA or in the femoral vein, and the inflow cannula is placed into the pulmonary artery, either directly or through a tubular graft extending outward from the second intercostal space.

TandemHeart is approved for ultrashort-term MCS and as a life-saving approach (as aa-ECCS) in the catheterization lab. Percutaneous t-MCS (*TandemHeart*) could be a more practical alternative due to not reopening the patient's chest. This system could be also used for vp-ECCS, and as well as for ECCPSs. The device consists of a small hydrodynamic centrifugal pump. It is a very versatile system providing easy deployment and discontinuation. For aa-ECCS, the left atrial cannulation is performed through a femoral vein and delivered across the atrial septum, and positioning is facilitated and confirmed by fluoroscopy or TEE guidance. Outflow is directed into the common femoral or axillary artery. Excellent left atrial decompression is obtained as long as the inflow cannula is approximately positioned. The standard percutaneous transseptal approach includes 21F inflow cannula and 17F arterial outflow cannula. However, larger cannulas could be used during surgically implantation and the size of the inflow cannula regulates pump flow between 4 and 8 L/min. Anticoagulation with low dose heparin to keep ACT below 200 s is sufficient while patients are on support. The atrial septum should be repaired when an LVAD is implanted. The most undesirable aspect of this device is that it requires complete immobilization of the patient.

6.2.2. Intracorporeal circulation support (ICCS)

Percutaneous t-MCSs are developed to unload the LV for better recovery and to maintain adequate CO in nonsurgical patients suffering from acute decompensated HF (acute cardiogenic shock), especially at bedside in the ICU or immediately in the catheterization laboratory [76]. A second application is short-term support of circulation during high-risk percutaneous or surgical cardiac interventions (coronary revascularization, mitral valve repair, etc.) in very sick patients without HF [77, 78]. The third indication could be transaortic left heart unloading in patients suffering from postcardiotomy syndrome treated with peripheral va-ECMO. The fourth clinical usage area is acute decompensation of end-stage HF to improve end-organ functions and to bridge to advanced HF treatments [79].

Impella is an axial-flow pump with three flow options (models 2.5 with flow 2.5 L/min, 5 with flow 5 L/min, CP with flow range between 3 and 4 L/min) and is suggested for t-MCS lasting up to five days [80]. This device is inserted percutaneously into the LV through the aortic valve. Models 2.5 and CP are implemented using 12F or 14F sheaths, respectively; however, model 5 requires surgical cut-down for a 21F catheter. The tip of the device is a pigtail that provides stabilization for the device in the LV. The pigtail connects by a cannula to a pump with a motor housing, intake (below the aortic valve) and output (above the aortic valve) areas, and a pump pressure monitor. The *Impella* device pumps blood directly from the LV into the

proximal aorta, thereby unloading the LV, increasing cardiac output, and improving mean arterial pressure, while reducing LVEDP, myocardial workload, and oxygen consumption [81]. The device is dependent on the left ventricular preload, and hence on satisfactory right ventricular function and adequate CVP (8–12 mmHg).

6.3. Permanent mechanical circulatory support (p-MCS)

Use of long-term MCS devices has grown more rapidly than expected in recent years due to disproportionately low number of donor hearts. Advanced technological improvements in permanent MCS, especially LVADs, increase patients' survival and quality of life. Whereas t-MCS devices are implanted as a short-term rescue treatment to keep patients alive as a bridge to more durable long-term MCS devices, p-MCS devices are implanted as a long-term survival and/or bridging treatment to HTx. In the last years, p-MCS has been accepted as a destination therapy for Stage-D HF, and several types of permanent supportive devices could be used for uni- or biventricular assistance. The indication interval has changed in the recent years and will change even more in the future, so that patients in better condition will be referred to LVAD therapy earlier for the purpose of achieving better outcomes. Patients with relative contraindication such as higher PVR, obesity, or tobacco usage may be switched to eligible transplantation candidates over time. Compared with pulsatile flow devices, continuous flow technology has led to notable improvements in survival and reduction of adverse events, as well as in renal and hepatic function as a result of hemodynamic support.

6.3.1. Ventricular assist device (VAD)

The best technological developments happened in HF therapies, especially surgically. The benefits of different surgical treatment options are depend on underlying causes, and coronary revascularization, valve interventions, or defect repairs can achieve the recovery in early-stage HF. The variety and efficiency of options for surgical intervention decreases with advanced stages, and new surgical strategies must be used to keep patients alive and to provide them with better quality of life. The last step of Stage-D HF surgery is HTx. On the other hand, LVAD implantation has been accepted as a new therapy option for Stage-D HF as destination therapy for older or those who are not otherwise suitable for HTx. Usage of LVAD is promising, will continue to grow, and has become a standard therapy for advanced HF as a bridge to recovery, as a destination therapy, and as a bridge to HTx [82].

A shift from the concept of TAH as heart replacement, toward the development of single-chamber pumps provided the impetus for development of p-MCS devices. In the past decade, ventricular assist device (VAD) systems showed a substantial progress in miniaturization, durability, reliability, and noise emission (**Table 21**) [83]. These devices ensure an adequate and regulable additional blood flow in parallel with the particular ventricle. They can be used either as an isolated LVAD or right ventricular assist device (RVAD) or biventricular VAD. *First generation* VADs were either pneumatically or electrically driven membrane pumps, generating hydrodynamically pulsatile flow with artificial heart valves as the inlet and outlet. *Second generation* VADs with reduced size consists of a rotary pump

Device type	Name	Assist	Mechanism
1st generation extracorporeal pulsatile devices	Thoratec PVAD	BV	Pneumatic pump
	Excure (Berlin Heart)	BV	Pneumatic pump
1st generation intracorporeal pulsatile devices	Thoratec IVAD	BV	Implantable version of Thoratec pVAD
	HeartMate IP, HM VE, XVE	LV	Pneumatic, electric vented pump
	Novacor	LV	Pulsatile
2nd generation continuous axial flow devices	EvaHeart LVAS	LV	thromboresistant coating
	Micromed DeBakey VAD	LV	Axial flow pump
	Jarvik 2000 Flowmarker	LV	Axial flow, intracardiac located small pump
	HeartMate II	LV	Axial flow pump
3rd generation continuous centrifugal pumps	Arrow CorAide	LV	
	ReliantHeart HeartAssist 5	LV	Axial, child version is FDA approved.
	Incore (Berlin Heart)	LV	Magnetically suspended axial flow
	Ventr-assist (Ventracor)	LV	Hydrodynamically suspended rotor
	Duraheart	LV	Magnetically suspended centrifugal pump
	HeartWare HVAD	BV	Miniature hydromagnetically suspended rotor
	HeartMate III	LV	Magnetically suspended centrifugal pump
	HeartWare MVAD	BV	development-stage miniature device
Total artificial heart	Abiocor	-	Pulsatile, motor driven hydraulic system
	CardioWest (Syncardia)	BV	Pulsatile, pneumatic pump, mechanical valves
	Carmat	BV	Pulsatile, pneumatic pump, biological valves

Table 21. The characteristics of long-term devices.

(impeller) with axial-flow design electromagnetically generating continuous flow without prosthetic valves, air vents, and compliance chambers. *Third generation* VADs eliminate bearings by using either hydrodynamic or electromagnetic suspension of an impeller. They employ a radial pump with both suspension mechanisms for contact-free rotation of an impeller that centrifugally generates continuous flow to reduce mechanical wear and trauma to blood cells.

Successful long-term outcomes after LVAD implantation are highly dependent on the timing of surgery (**Table 4**) and HF criteria (**Table 11**). If the LVAD is implanted too late, the outcome may worsen due to end-organ damage caused by prolonged HF (e.g. from poor nutritional status, low serum albumin, impaired liver- and renal function, markers of RHF). Long-term survival is best for patients with INTERMACS level 3 to 5, and worse for patients with INTERMACS level 1. With third generation LVADs (HeartWare or HeartMate III), early and mid-term survival has improved (>85% for 6 months and 1 year) with lower complication rates.

Five-year survival is approximately 60% with HeartWare device [84]. Absolute contraindications for LVAD implantation are obstructive or restrictive CMPs, irreversible lung or liver damage, active infection, aortic regurgitation, and severe RVF. Relative contraindications are increased risk of bleeding, cerebral ischemia, irreversible kidney damage, and prior implantation of mechanical aortic valve prosthesis [85].

6.3.2. Total artificial heart (TAH)

Total replacement of the biventricular-failed heart with a total prosthetic heart is unlikely to see widespread usage due to the extraordinarily aggressive nature of the surgery. Several complicating factors can constrain the implantation of these devices: patient characteristics, device size, implantation timing and location, and the need for extensive surgery. Implantation of LVAD alone could aid these patients because of its ability to partially right ventricular functions, and this advantage makes the LVAD approach generally preferred over TAH in patients with biventricular failure. The usage of TAH devices is restricted to the patient's in whom LVAD is not feasible due to infiltrative or restrictive CMPs, cardiac malignancies, nonsurgical postinfarction ventricular septal defect, intractable ventricular arrhythmias, and cardiac graft failure [86]. The device has two artificial ventricles lined with polyurethane, and ejects blood via a four-layer, moving diaphragm driven pneumatically or hydraulically [87]. The ventricle cuffs are sutured to patient's atria and outflow grafts to the aorta and pulmonary artery. The device has four mechanical or biological valves maintaining unidirectional flow. The implanted device is powered by a loud and very heavy external compressor. Thrombosis, thromboembolic events, postoperative bleeding, or infections are significant and relatively frequent complications. The other dissuasive structure can be double drivelines tunneled under the skin, but the drive unit can be set inside the patients' body. Both artificial ventricles alternately eject blood to balance left and right heart CO. There are certain sizing criteria for TAH implantation: chest antero-posterior distance >10 cm, body surface area >1.7 m², cardiothoracic ratio >0.5 , and LVEDD >66 mm.

7. Cardiac transplantation

Heart transplantation is the only curable and durable treatment option for HF, especially with new immunosuppression therapies, improved clinical management, and pharmaceutical development for refractory or end-stage HF. The most common indication is dilated CMP (50%), and the second is ischemic CMP (35%), but retransplantation ratio has not changed (3%) in the last decade. Once patients are approved for HTx, they are listed according to the medical urgency status and severity of the illness (**Table 22**). Worldwide, a steady decline in heart transplantation has been observed over the last 15 years due to a one-third decrease in the availability of donor organs, while the numbers of patients awaiting heart transplant has doubled. About 15–20% of patients listed for transplantation die before a suitable organ becomes available and more than 30% of patients awaiting HTx require an appropriate MCS to bridge to transplant. The median waiting time for HTx in several countries is

Code status	Description
1A	<ul style="list-style-type: none"> - Patients in the intensive care unit with inotropic support + mechanical support (ECMO, ECCS) ± respiratorial support + a pulmonary artery catheter for hemodynamic monitoring - LVAD patients with <ul style="list-style-type: none"> - life-threatening ventricular arrhythmia - right ventricular failure - device malfunction/mechanical failure, thromboembolism, infection - RVAD - LVAD < 30 days - TAH
1B	<p>Patients who are on inotropic support but not meeting 1A criteria</p> <p>Patients have a ventricular assist device longer than 30 days</p>
2	Patients who are waiting at home on medical therapy
7	Patients who are on hold because of an intervening medical illness, making them inappropriate candidates for transplantation

Table 22. Transplantation urgency code status.

approximately 6 to 9 months and depends on several factors, including listed status, body weight, blood group, and differences between recipient and donor. Potential transplant recipients can have decompensated HF requiring high-dose pharmacological treatment and/or MCS, symptomatic Stage-D HF under optimal medical therapy, asymptomatic advanced HF with a peak VO_2 of less than 15 mL/kg/min, or recurrent arrhythmias despite interventions. Maximal VO_2 is the most noninvasively valuable test for better evaluation of potential recipients, and a peak VO_2 of less than 12 mL/kg/min indicates a poor prognosis. The most variable relative contraindication among centers is the age limit; however, transplant guidelines extend the eligibility to 70 years of age, leading individual centers to determine their own age cut-off. Malignancy, impaired lung and renal functions can increase morbidity and impair prognosis. Patients with presenting fixed PAH are associated with high early mortality, and should be considered for combined heart-lung transplantation. Nevertheless, it has been shown that a continuous flow LVAD may help to reduce PVR, so that the patient becomes eligible for subsequent cardiac transplantation. The number of HTx recipients on MCS has doubled and reached 45% of total HTx candidates in the last decade (>50% in 2014): LVAD 85.2%, RVAD 7.2%, TAH 3.1%, and ECMO 2.9% [88]. Patients implanted with a LVAD on status 1A because of device complications or a 30-day elective grace period or on Status 1B will be priority to receive the organ unless they are deemed nontransplantation candidate (Status 7). It has been reported that approximately more than 50% patients were in Status 1A, and one-half patients had LVAD with in Status 1A (70%) or 1B (30%) at the time of HTx; whereas one-third of the patients in Status 1A had LVAD, of which 50% had device complications, and one-fifth patients in Status 1B had LVAD [89].

Early (<30 days) mortality ranges from 5% to 10% usually due to primary graft failure (35.3%), multiple organ failure (21.6%), and infection (14.3%); and 1-, 2-, 3-, 4-, 5-, 10-, and 15-year cumulative survival rates are 82, 78, 75, 72.5, 69.5, 52, and 34.4%, respectively [88]. A decline in 1-year overall survival after HTx from 85 to 76% in the EuroTransplant region has been observed, presumably because of increasing donor age and recipient comorbidity [90]. Early mortality and long-term survival rates in recipients assisted by ECMO are worse than those assisted by LVAD: early mortality is 35 versus 5%, and 1-, 2-, 3-, 4-, and 5-year survival rates are 60 versus 89%, 54 versus 86%, 51.5 versus 82%, 51.5 versus 81%, and 51.5 versus 76%, respectively [88]. The one-year survival after HTx is similar in patients with LVAD (89%), but complicated postimplant recipients have worse, 3-year survival than noncomplicated postimplant recipients (78 versus 85%) [89]. Long-term survival is dependent on several factors, but the availability of the donor hearts from younger male donors with shortest ischemic times is identified as the most significant factor improving long-term survival [91]. The median survival is at least 13.5 years for patients who survive the first year. Survival is lower in patients with valvular cardiomyopathy, congenital heart disease, or following retransplantation, and for those requiring pretransplant MCS. Additionally, patients who are sicker prior to transplant have worse survival outcomes [92]. Cardiac allograft vasculopathy is among the primary causes of death after the first year of HTx, and it is the most important limiting factor in long-term survival, along with neoplasms, with an incidence of 8% in the first year, 30% in 5 years, and 50% in 10 years [93].

Heart transplantation surgery is not a complex procedure, and surgical implantation techniques are the easiest part of HTx. The main problem with HTx is cold ischemic time to donor heart transportation, which should be <4 hours without continuous coronary perfusion or >4 hours with coronary perfusion via special equipment. The ideal cold ischemic time is shorter than 2 hours. Second problem is immunosuppression to prevent organ rejection, which is the main risk factor for graft failure preoperatively and early postoperatively (<1 year), and thereafter cardiac allograft vasculopathy is the major problem after the first posttransplant year. Third problem is increased PVR and it should be managed aggressively, because the unprepared donor RV may be unable to overcome this increased afterload. The standard technique is orthotopic HTx. The great arteries are transected at the sinotubular junctions, whereas the LA is insised along the atrioventricular groove, leaving left atrial cuff for anastomosis. For biatrial technique, the RA is prepared with the same manner; however, for bicaval technique, both vena cavae are transected at their right atrial junctions. Bicaval anastomosis is a more common approach for implantation of the donor heart rather than biatrial technique [94]. The advantages of bicaval technique are reducing the right atrial size, preserving atrial conduction pathways, decreasing the risk of tricuspid regurgitation, and avoiding permanent pacemaker need [95]. Annuloaortic ectasia with the ascending aorta aneurysm could be managed by the replacement of the recipient ascending aorta during HTx [96].

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