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LONG-TERM MANAGEMENT OF END-STAGE HEART FAILURE

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Abstract

End-stage heart failure manifests as severe and often relentless symptoms that define the clinical syndrome of heart failure, namely congestion and hypoperfusion. These patients suffer from dyspnea, fatigue, abdominal discomfort and ultimately cardiac cachexia. Renal and hepatic dysfunction frequently further complicate the process. Recurrent hospitalizations, cardiac arrhythmias, and intolerance to standard heart failure therapies are common as the disease progresses. Management focuses on controlling symptoms, correcting precipitants, avoiding triggers, and maximizing therapies with demonstrable survival benefit. Amongst appropriate candidates, advanced therapies such as orthotopic heart transplant (OHT) can significantly extend survival and improve quality-of-life. Left ventricular assist devices (LVADs) have been used with increasing frequency as a bridge to OHT or as destination therapy in appropriately selected candidates where they have a demonstrable mortality benefit over medical therapy. Importantly, a multidisciplinary patient-centred approach is crucial when considering these advanced therapies.

Keywords

Heart Failure; cardiac resynchronization therapy; transplant; heart-assist devices

Background

Heart failure (HF) is a clinical syndrome manifested by vascular congestion and/or peripheral hypoperfusion in the setting of structural and/or functional cardiac abnormalities. Congestion commonly presents with dyspnea, reduced exercise tolerance, and edema while hypoperfusion results in end-organ dysfunction. (1, 2) Importantly therefore, it is a clinical diagnosis in the setting of an underlying cardiac disturbance (pericardial, myocardial, valvular, or metabolic) and thus the left ventricular (LV) ejection fraction may be reduced (HFrEF, LVEF < 40%) or preserved (HFpEF, LVEF ≥ 50%). (1) Common causes of HF are

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outlined in Table 1. Those with LVEF 41–49% represent an intermediate category for which the management strategy is less clearly defined.

End-stage, or ‘advanced’ HF (ACC/AHA stage D) is characterized by progressive and/or persistent, severe symptoms, recurrent decompensations, and severe cardiac dysfunction despite medical optimization.(2, 3) It is estimated that approximately 5% of HF patients are stage D.(4) However, given the 26 million people with HF worldwide,(5) these patients nonetheless comprise an important group and one for whom 1-year mortality can be as high as 75%.(6) These patients suffer from dyspnea at rest or with minimal exertion, fatigue, gastrointestinal symptoms, cachexia, anxiety and depression. The management of this complex patient population will be the focus of this chapter.

Pathophysiology

HF is characterized by impairment in cardiac structure and function which, in its advanced phases, results in decreased cardiac output (hypoperfusion) and/or fluid buildup (congestion).(1, 2) Initially cardiac output (CO) is maintained through the Frank-Starling mechanism with LV dilation and wall thickening. Eventually myocardial contractility declines and stroke volume decreases.(7) A compensatory increase in heart rate may initially help maintain cardiac output, but this too will ultimately fail to preserve output. The two principal pathways mediating the pathophysiology of heart failure are the sympathetic nervous system (SNS) and the renin-angiotensin system (RAS). These systems are innately related, having the ability to further activate each other and ultimately resulting in a chronic state of increased effective circulating volume. Over time, myocardial alterations result in reduced responsiveness to these adaptive mechanisms, and thus a drop in cardiac output ensues. Not surprisingly the principal HF therapies target these pathways, and hence an understanding of these systems is imperative to HF management.

Sympathetic Nervous System (SNS) activation

Under normal circumstances, the SNS is inhibited by the high-pressure baroreceptors and low pressure mechanoreceptors in the heart. In HF however, these inhibitory mechanisms are diminished due to increased pressure in the LV and reduced pressure at the level of the baroreceptor, resulting in over-activation of the SNS. Early on, this augments heart rate and contractility, helping to maintain cardiac output. However ultimately beta-adrenergic responsiveness decreases and norepinephrine (NE) stores are depleted, while increased hypertrophy, fibrosis, and myocyte necrosis ensue.

Renin-Angiotensin System (RAS) activation

Renal hypoperfusion and constitutive SNS activation results in increased renin release from the kidney and thus activation of the RAS system with angiotensinogen in the liver being converted to angiotensin I, which is cleaved to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II causes sodium (and water) retention at the level of the kidney, vasoconstriction, ADH release (resulting in thirst), and aldosterone secretion that in turn promotes further sodium retention, hypertrophy, and fibrosis.

The Hemodynamics of HF

The four classical hemodynamic profiles of heart failure can be categorized in a two-by-two matrix based on filling pressures (presence or absence of congestion) and perfusion status. (adequate/inadequate).(8) Patients with advanced HF typically live in a fine balance between the “wet and warm” (i.e. relatively preserved perfusion but congested) and “wet and cold” (i.e. low perfusion and congested) categories. Elevated left sided filling pressures result in subendocardial ischemia as a result of a decreased coronary perfusion gradient and mitral regurgitation as a result of annular dilatation, which in turn further lowers cardiac output.(9) If high enough, these filling pressures result in frank pulmonary edema but otherwise may manifest as exercise intolerance and fatigue. Moreover, elevated left sided filling pressures lead to high pulmonary pressures, the so called ‘group 2’ pulmonary hypertension.(10) Over time, this leads to pulmonary vascular remodelling resulting in an inability to reduce the pulmonary pressures with vasodilator challenge.(3)

Invasive hemodynamic assessment is typically required to 1) diagnose pulmonary hypertension and its reversibility in patients undergoing transplant work-up 2) assess the adequacy of RV function in patients being considered for LVAD, 3) assess qualification for home inotropic support and 4) clarify hemodynamic status when it is not clear based on clinical features (e.g. combined sepsis and cardiogenic shock). The ESCAPE trial did not show superiority of Swan-Ganz guided management amongst hospitalized patients with advanced HF in terms of days outside hospital over the subsequent 6 months, resulting in a shift away from this type of hemodynamic monitoring.(11) However, several points are of note. First, clinicians were discouraged from using inotropes, a central component of hemodynamic tailoring. Second, the study demonstrated a strong trend towards better outcomes in terms of quality-of-life measures. Third, few patients went on to advanced therapies, where achieving a fine balance between diuresis and worsening renal function is essential. Finally, as for any procedure, outcomes were better at centres with higher volumes.

More recently, there has been a resurgence of interest in hemodynamic monitoring using the implantable CardioMEMS sensor that allows for day-to-day assessment of pulmonary artery pressures. The results are transmitted to the overseeing physician allowing for medication adjustment. The CHAMPION trial demonstrated a significant reduction in HF hospitalizations with this system, and further trials are ongoing.(12)

Approach to the Management of Advanced HF

The management of advanced HF begins with 1) confirming that the patient’s clinical picture is consistent with advanced HF and 2) addressing treatable and/or reversible causes (ex. thyroid disease, ischemia). After confirming the clinical syndrome of advanced HF, the central principles of management focus on treating symptoms, delaying progression, avoiding decompensations, and managing comorbidities. In tandem with this, is the continual assessment of the need for advanced therapies, principally orthotopic heart transplant (OHT) and/or left ventricular support device (LVAD). These topics will be covered in subsequent chapters. The overarching goal is to improve quality-of-life and prolong survival. What follows is an approach to the management of end-stage HFrEF.

Confirming Advanced HF

The ACC/AHA definition of advanced HF is comprised of a constellation of 11 clinical variables including recurrent hospitalizations, frequent ICD shocks, severe exercise limitation, hypotension, weight loss, the need to escalate diuretics or reduce RAAS inhibition/beta-blockers, hyponatremia, and worsening renal function. The European Society of Cardiology definition also includes more objective measures of severe cardiac dysfunction including LVEF<30%, RAP>12, PCWP>16, high BNP, 6-MWT distance 300m, and peak VO₂<12–14mL/kg/min (Table 2). Regardless of the definition used, these features define the clinical syndrome of advanced HF as distinct from predominant severe pulmonary or renal disease with a non-dominant cardiac contribution.

Addressing Reversible Aetiologies

Ischemia

The hallmark study addressing the role of revascularization (CABG) versus medical management in advanced HF was the STITCH trial, which, on first glance was negative for the primary endpoint of all-cause mortality (41% for CABG vs. 36%, medical therapy, $p=0.12$). However, revascularization was superior to medical therapy for the endpoint of death from cardiovascular cause and the composite of all-cause mortality or hospitalization. Moreover, crossover rates were high with 17% in the medical therapy group undergoing CABG. In as-treated analysis there was a statistically significant mortality reduction with CABG.(13) More recently, the 10-year follow-up of STITCH was published confirming a statistically significant mortality benefit in the group who underwent CABG in addition to medical therapy.(14) These findings provide strong argument for the benefit of revascularization in patients with HFrEF, however, the number of patients with advanced HF was low and the operative risk in this group is high. Recently, the AWESOME trial compared CABG vs. PCI in high risk surgical candidates and found PCI to be equivalent to CABG in terms of survival.(15) In some cases it may be reasonable to assess viability to assist in decision making, although viability testing per se has not been conclusively found to predict outcomes.(16, 17) The SYNTAX II score combines anatomical and clinical variables and may be useful when deciding on the revascularization strategy.(18) Ultimately a multidisciplinary “heart team approach” including a cardiologist, interventionalist, and surgeon is advised.(19)

Other common reversible aetiologies

Important other reversible/correctable aetiologies include tachycardia (i.e. due to tachyarrhythmia), thyroid disease, alcohol, illicit drugs (cocaine, amphetamines), certain chemotherapies (ex. trastuzumab), and valvular disease.(20, 21) In the latter case, one must decide if the valvular dysfunction is primary (i.e. due to an intrinsic problem with the valve or valvular apparatus), in which case corrective intervention may allow for full ventricular recovery. In contrast, if mitral regurgitation is secondary to ventricular dilation, the evidence for correction is less well established and the risks may outweigh the benefits. In addition, medical therapies (discussed below) with beneficial effects on ventricular remodelling may reduce or even eliminate regurgitation.(21)

Medical Management of Advanced Heart Failure

The cornerstone of HF medical therapy lies in the inhibition of the RAS and sympathetic nervous system. The main therapies have until recently been comprised of the triad of ACE inhibitors (or angiotensin receptor blockers [ARB] if intolerant), beta-adrenoreceptor antagonists (beta-blockers), and mineralocorticoid receptor antagonists (MRAs) titrated to target doses. All three have demonstrated mortality benefit in HFrEF. Titration is achieved by sequentially adding each class starting with low doses and uptitrating over 4–6 months. Two newer medical therapies have been developed that are now approved for patients who remain symptomatic despite the above triple therapy combination. The first is a neprilysin inhibitor-ARB combination (sacubitril-valsartan) while the other is a selective I_f current inhibitor that slows heart rate.

Unfortunately, in advanced HF, medical optimization is often not tolerated as a result of worsening hypotension, hyperkalemia, and renal dysfunction. It is then not surprising that the need to reduce the dose or eliminate these therapies is an established marker of poor prognosis.

ACE Inhibitors

ACE inhibition prevents the conversion of angiotensin I to angiotensin II by ACE thus attenuating the sodium retention, vasoconstriction, SNS activation, and remodelling induced by RAS activation. ACE inhibitors have demonstrated benefit in all classes of heart failure including asymptomatic LV dysfunction. However, the benefit is greatest amongst those with more severe (NYHA class IV) symptoms as evidenced by the 31% one-year mortality reduction in the CONSENSUS trial.(22) This effect is largely achieved through a reduction in progressive HF (as opposed to sudden cardiac death [SCD]). Moreover, functional status and LV dimensions improved highlighting their role in the long-term prevention of negative remodelling.(22)

Side effects include hypotension, azotemia, and hyperkalemia which are usually mild. However, in advanced HF these can be marked requiring downtitration and ultimately discontinuation.(3) In general, a low-potassium diet in addition to careful early monitoring of renal function and potassium levels help prevent hyperkalemia.(1) Hypotension may be minimized by taking longer acting formulations (e.g. lisinopril) at night. In addition to inhibiting the RAS pathway, ACEI also reduce bradykinin breakdown, which in rare instances can result in life threatening angioedema (1%) or a non-productive cough (10–15%).

Angiotensin Receptor Antagonists (ARBs)

Angiotensin-receptor blockers inhibit the RAS by blocking the interaction between angiotensin II and the type 1 angiotensin (AT-1) receptor. As a result, they do not interfere with the breakdown of bradykinin and thus do not cause the cough associated with ACEI. Their efficacy in heart failure was demonstrated in the CHARM-Alternative (Candesartan) and Val-HeFT trials. (23, 24) However, few patients were NYHA class IV in either trial. CHARM-Added addressed the question of whether combining an ACEI and ARB would

provide additional benefit.(25) The reduction in cardiovascular mortality and HF hospitalization were limited by worsening renal dysfunction and hyperkalemia. Moreover, few patients were on a mineralocorticoid receptor antagonist (see below), which further exacerbates hyperkalemia. As such, in practice this combination is rarely used except in patients who are unable to tolerate a mineralocorticoid receptor antagonist (discussed below).(1)

Beta-adrenoreceptor antagonists (beta-blockers)

Beta-blockers represent a major breakthrough in the timeline of heart failure therapy. After early concerns of worsening cardiac output (through effects on heart rate and contractility) their benefit on mortality, symptoms, and LV remodelling have been clearly demonstrated. (26, 27) These results were extended to the advanced HF population in the COPERNICUS trial (NYHA III–IV, LVEF<25%) with a 38% mortality risk reduction at 12 months.(28) Importantly, unlike ACEI, the benefits of beta-blockers are not a class effect. Rather, only carvedilol, bisoprolol and metoprolol XL have demonstrable mortality benefit and thus are the recommended therapy of choice. Moreover, beta-blockers reduce mortality not only from progressive HF but also SCD. From a management perspective, beta-blockers should only be initiated once the patient is euvolemic, and should be uptitrated slowly. Generally, the ACE inhibitor is added first, although the converse can be done as well.(29) Beta-blockers should not necessarily be discontinued during an episode of decompensation unless the patient is in cardiogenic shock.(1)

Mineralocorticoid receptor antagonists (MRAs)

Unlike ACEI, ARBs, and beta-blockers, the benefits of MRAs were first demonstrated in the advanced HF population and then broadened to milder degrees of HF. In the RALES trial, spironolactone resulted in a 30% mortality reduction and 35% reduction in HF hospitalizations amongst patients with NYHA III–IV symptoms and LVEF<35%.(30) These effects are in addition to the upstream inhibition of RAS by an ACEI or ARB, likely as a result of aldosterone levels quickly returning to baseline after initiation of one of these upstream therapies. MRAs are believed to play an important role in the prevention of extracellular matrix remodelling. Moreover, they act as a potassium sparing diuretic in the distal tubule. As a result, they should not be started in patients with a creatinine clearance <30 mL/min or potassium >5.0mmol/L.(1) Patients must be advised of the importance of a low potassium diet or, if currently receiving potassium supplementation, this should be discontinued and renal function/potassium should be checked within 1 week and frequently thereafter until stability is achieved. Gynecomastia affects ~10% of men taking spironolactone and can be overcome by switching to eplerenone.

Sacubitril-Valsartan

After a repose in the evolution of medical therapies for HF, the publication of PARADIGM-HF set a new standard for the management of symptomatic HFrEF. Specifically, as compared with enalapril, the combined neprilysin inhibitor/ARB sacubitril-valsartan reduced the primary composite of cardiovascular mortality or HF hospitalization by 20% as well as demonstrating a 16% reduction in all-cause mortality.(31) Neprilysin breaks down natriuretic peptides, which counterbalance RAS while valsartan blocks the downstream

consequences of RAS inhibition at the level of the AT 1 receptor thus maintaining counter-regulation and providing blockade of the constitutively active RAS system in HF. Of note, patients had to tolerate a run-in period of target dose enalapril 10mg BID limiting inclusion of many advanced HF patients. Indeed <1% were NYHA class IV with most being class II. Moreover, the main side effect was hypotension. Nonetheless, guidelines suggest that secubitril-valsartan be considered in patients who remain symptomatic despite triple therapy (ACEI/beta-blocker/MRA).(2, 32)

Ivabradine—Ivabradine is a selective pacemaker current inhibitor working at the level of the SA node to slow heart rate. Ivabradine reduced the composite of cardiovascular death or hospitalization for worsening HF amongst symptomatic patients with LVEF<35% who were in sinus rhythm with a heart rate >70bpm despite maximum tolerated doses of standard medical therapies (including beta-blockers).(33) Importantly, this was driven mainly by a reduction in hospitalizations as there was no demonstrable mortality benefit. Although mean LVEF was 29% and half the patients were NYHA class III, in truly advanced HF, tachycardia is a compensatory mechanism to maintain cardiac output and thus careful patient selection is necessary. Indeed, the ACC/AHA 2016 Focused Heart Failure update suggests consideration of ivabradine only for NYHA class II and III patients with LVEF<35, in sinus rhythm with HR>70bpm on maximum tolerated doses of a beta-blocker.(32)

Adjunctive Therapies & Non-pharmacologic management

Diuretics & Fluid restriction

Central to the management of advanced HF is volume status, both in terms of symptom control and preventing decompensations. Euvolemia (or as near to it as feasible) is maintained with fluid restriction (1.5–2 L/day) and loop diuretics. Furosemide is commonly used. However, its oral bioavailability is lower than the other members of this class namely bumetanide and torsemide which, in advanced HF, may be required.(1, 2) In the setting of diuretic refractoriness, metolazone or chlorthiazide which potentiate the action of loop diuretics at the level of the distal convoluted tubule may be added.(2)

Digoxin—Digoxin is a cardiac glycoside with mild inotropic properties resulting from its ability to inhibit the Na/K-ATPase, with the ultimate effect being an increase in intracellular calcium. In the DIG trial, there was no mortality benefit but digoxin was associated with a decrease in hospitalization for worsening HF.(34) Importantly, there is a narrow therapeutic window and population based studies have raised concerns about increased mortality.(35) However, in HF the optimal serum level is only 0.5–0.9ng/mL. As such, typically the lowest dose or an alternate day dosing strategy is used in conjunction with close monitoring of renal function.(1)

Hydralazine/Isosorbide Dinitrate

The importance of vasodilation in HF was noted relatively early in the timeline of HF management. The V-HeFT trial (1986) demonstrated a mortality benefit not quite reaching statistical significance for the combined arterial/venodilator combination of Hydralazine/ISDN but this was quickly overshadowed by the superiority of enalapril in V-HeFT-2.(36,

37) However, in advanced HF where renal dysfunction is common, hydralazine/ISDN may be used when ACE inhibitors or ARBs are not tolerated. Moreover, owing to the mortality benefit amongst black patients with advanced (NYHA III and IV) HF demonstrated in the A-HeFT trial, hydralazine/ISDN should be added to standard therapies in all black patients who tolerate it hemodynamically.(38)

Electrophysiological interventions in HF

Implantable Cardioverter-Defibrillators (ICDs)

Death from heart failure can occur suddenly from a lethal arrhythmia or due to pump failure with progressively worsening symptoms of congestion and hypoperfusion. While ICDs have been shown in large randomized trials to reduce mortality when used both in patients with documented ventricular arrhythmias (2° prevention) or prophylactically (1° prevention), it is important to note that patients with NYHA class IV symptoms were excluded from these trials.(39–41) Moreover, benefits were generally seen after 1 year.(42) Of equal note is the fact that ICDs do not change the course of the disease process itself but rather reduce mortality by aborting sudden cardiac death from an otherwise lethal arrhythmia. Thus careful consideration is advised when deciding to implant an ICD in an advanced HF patient unless they are being considered for transplant.(1, 42) In certain cases, a wearable external defibrillator (Lifevest) may be considered.(42) The utility of ICDs in patients with continuous flow LVADs remains controversial but may be beneficial amongst those with a history of ventricular arrhythmias.(43, 44)

Cardiac Resynchronization Therapy (CRT)—Unlike ICDs, cardiac resynchronization therapy (CRT) can improve ventricular geometry, reverse remodelling, reduce secondary mitral regurgitation, and increase LVEF with resulting objective clinical improvement in exercise capacity and a demonstrable mortality benefit in symptomatic patients who are in sinus rhythm, with a left bundle branch block, QRS width >150msec, and LVEF <35%.(45, 46) These trials did include ambulatory NYHA class IV patients.(47) It should be emphasized that not all patients respond and the procedural risks must be weighed against the benefits. However, because of the clinical improvement amongst responders, CRT can also be considered for patients who do not wish or qualify for an ICD.(2)

Addressing comorbidities and Consequences

There is a myriad of comorbidities common in HF patients that may contribute to the pathology of the cardiomyopathy itself and/or the patient's clinical status. These are, in general, associated with worse outcomes. Pre-existing comorbidities are often compounded by the consequences of advanced HF, resulting in severe end-organ dysfunction.

Sleep apnea

Sleep disordered breathing (both central and obstructive) is common in chronic HF and is associated with higher NYHA class.(1) Importantly, treatment of obstructive sleep apnea reduces LV end-systolic dimension and improves LVEF.(48, 49)

Atrial fibrillation

Atrial fibrillation affects up to 40% of patients with NYHA class IV symptoms. Rate or rhythm control may be used with beta-blockers being the mainstay in the former case, while amiodarone and cardioversion are the preferred treatment when the latter strategy is chosen. Some patients may have worsening heart failure symptoms while in atrial fibrillation irrespective of heart rate, and for this subset of patients, greater efforts to maintain sinus rhythm may be employed. Nondihydropyridine calcium channel blockers should not be used. Given that heart failure is a risk factor for embolic events for patients with atrial fibrillation, anticoagulation is typically recommended for patients who tolerate it.(1, 50)

Cardiorenal interactions

Renal dysfunction is a common occurrence in advanced HF and is associated with worse outcomes.(3) Reduced renal perfusion and/or increased congestion with or without intrinsic renal disease contribute to its pathology. Notably, patients with severe renal dysfunction have been excluded from most major trials and thus, less is known about the efficacy of standard medical therapies amongst these patients.(2) Cut-offs for advanced therapies remain questionable, however, proteinuria and eGFR<40 have been associated with worse outcomes after LVAD.(51)

Hepatorenal interactions

Hepatic dysfunction in heart failure can be due to congestion or hypoperfusion (ischemia) and may ultimately result in cirrhosis.(3) Patients with hepatic dysfunction have worse outcomes including higher mortality.(52) Using the MELD score may improve prognostication.(53)

Hyponatremia

Hyponatremia, resulting in part from increased arginine vasopressin, is a marker of adverse prognosis in advanced HF and can result in cognitive dysfunction.(1) Tolvaptan, a selective V2-receptor antagonist, was not shown to improve long-term outcomes in hospitalized patients with HF. However, improvements in serum sodium, dyspnea, and weight loss were observed.(54, 55) As such, its use is recommended in hyponatremic, symptomatic patients with volume overload despite fluid restriction and optimal medical therapy.(1)

Iron deficiency & anemia

Up to 50% of patients with advanced HF suffer from anemia which is associated with increased hospitalization and reduced survival.(56) Decreased cardiac output and hence renal hypoperfusion with the ensuing RAS and inflammatory cascade activation, decreased bone marrow erythropoietin (EPO) response, and CKD with associated reduced EPO production all contribute to the pathophysiology.(56) After ruling out other aetiologies (e.g. colorectal cancer), patients who are iron deficient should receive intravenous iron supplementation to improve functional capacity and quality of life.(57, 58) However, in the absence of chronic kidney disease, EPO should not be routinely administered given the lack of benefit and increased risk of thromboembolic complications.(59)

Comprehensive Management of Refractory (End-stage) HF: An Approach

After treating reversible causes, optimizing medical therapies/CRT, and managing comorbidities, the persistently symptomatic patient is said to have advance HF and the focus turns towards defining the optimal therapeutic approach. Options include orthotopic heart transplant (OHT), left ventricular assist device (LVAD) and/or palliation. Ultimately, a combination of these three strategies is often required. A framework is presented in Figure 1.

General measures

A patient empowered approach is central to the management of advanced heart failure. It is not surprising then that Disease Management Programs, which assist patients and empower them to take control of their symptoms have been shown to reduce HF hospitalizations.(60) Managing volume status requires meticulous attention to fluid restriction (<2L and in some cases <1L/day), daily weights, and adherence to a low sodium diet.(1, 2) Indeed, dietary indiscretions are one of the most common precipitants of a HF decompensation. Exercise programs have also demonstrated a reduction in HF hospitalizations and improvement in quality-of-life.(61, 62) Additional measures common to chronic disease management include influenza and pneumococcal vaccination, as well as smoking cessation.(1)

Triggers for Advanced Therapies

There is no one marker that identifies the need for advanced therapies. However, several clinical, biochemical, and hemodynamics parameters have been identified as triggers that should prompt further assessment. Scoring systems such as the *Heart Failure Survival Score* and the *Seattle Heart Failure Model* have been developed but subsequently found to have only modest discriminatory ability and may underestimate mortality risk.(63–67)

From a clinical perspective, peak VO_2 <14mL/kg (<11mL/kg on a beta blocker) is a powerful predictor of outcome as are recurrent hospitalizations and the need to withdraw RAS antagonists or beta-blockers.(63, 67) Biochemical parameters of end organ dysfunction, hyponatremia and an elevated BNP are similarly concerning. Hemodynamic findings of persistently elevated pulmonary capillary wedge pressure, pulmonary hypertension, and worsening right heart failure are similarly worrisome. Any combination of these findings should trigger specialized referral for advanced therapies.(3)

Once the need for advanced therapies has been determined the next step is to assess patient readiness to proceed. Unlike other conditions, HF is characterized by a series of hills and valleys where decompensations are interspersed with periods of relative stability and although the overall trajectory is downwards, compensatory mechanisms on the part of the patient may obscure their perception of this.(68) Moreover, it should be emphasized that both transplant and LVAD, while life prolonging are not curative but rather a trade-off for a new set of complications. However, amongst those patients who are motivated to proceed, the next step is to carefully assess transplant candidacy and/or the need for LVAD therapy.

Assessing transplant candidacy

While programs vary in their listing criteria, key considerations include age, pulmonary hypertension, irreversible end organ dysfunction, comorbidities, frailty, and substance abuse/psychosocial issues.(69) The consensus guidelines for selection of patients for heart transplantation are discussed in Chapter 5.

Evaluation of the patient being considered for LVAD

Historically, LVADs were implanted to support patients awaiting cardiac transplantation. The REMATCH trial demonstrated the survival benefit with LVAD over inotropes in transplant-ineligible candidates, and the FDA approved LVAD use as destination therapy (DT) and added a life-saving option for patients for whom palliation was previously the only one.(6)

Compared to transplant, the contraindications to LVAD are slightly less stringent. Nonetheless, outcomes vary and scoring systems have been devised to improve patient selection. Specific considerations include assessment of RV function, body surface area, end organ dysfunction (renal and hepatic), bleeding risk, frailty, and adequacy of social supports. (70, 71)

Home Inotropic Support

While long-term outcomes on home inotropic support remains poor with estimated 1-year survival ranging from 6%–11%, they continue to play a role in selective patients either as bridge to transplant or for palliation.

Palliative Care

Palliative care is an approach that improves quality-of-life for patients and their families in the setting of life-threatening illness. End stage HF is characterized by a myriad of distressing symptoms making palliative care an essential component of the patient centred approach. Dyspnea, related not only to fluid overload but also skeletal myopathy is common, along with fatigue, anxiety and depression.(72) Gastrointestinal symptoms are likewise common often due to elevated filling pressures, which further exacerbate the cardiac cachexia that heralds the presence of end-stage disease. Pain is a prevalent symptom with studies documenting a frequency of up to 84%.(73) The need to continually address these symptoms makes palliative care an integral part of end-stage HF management irrespective of whether advanced therapies are being pursued.

Summary

Advanced heart failure is defined by refractory symptoms of congestion and/or hypoperfusion. Medical therapies with proven mortality and morbidity benefit include ACE inhibitors or ARBs along with beta-blockers and MRAs. More recently, sacubitril-valsartan, a combined neprilysin/ARB, has demonstrated a mortality benefit. Cardiac resynchronization therapy may significantly improve symptoms and outcomes in

appropriately selected candidates. Triggers for advanced therapies, namely LVAD and/or transplant, include clinical parameters such as recurrent hospitalizations, frequent ICD shocks, escalating diuretic requirements, and intolerance to medical therapies. Throughout the process, a multidisciplinary approach with meticulous attention to symptoms and patient preferences is essential for the management of this diverse and complex patient population.

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Practice Points

- Management of advanced HF is focused on symptom control, treating correctable causes or precipitants of worsening clinical status, and optimizing therapies with proven mortality benefit
- Standard medical therapies for HFrEF include Angiotensin-converting-enzyme inhibitors (ACE inhibitors), beta-blockers, mineralocorticoid receptor antagonists (MRAs) although their use is often limited by hypotension or worsening renal dysfunction
- Cardiac-resynchronization therapy may benefit appropriately selected candidates
- Newer therapies include the combined neprilysin inhibitor/angiotensin-receptor blocker Sacubitril-Valsartan and the SA-nodal blocker Ivabradine, although their role in truly advanced heart failure is less well established
- Triggers prompting referral for advanced therapies (transplant or LVAD) include recurrent hospitalizations, frequent ICD shocks, escalating diuretic requirements, intolerance to standard therapies, extremely limited functional capacity (peak $\text{VO}_2 < 14 \text{ ml/kg/min}$, 6-MWT $< 300 \text{ m}$), elevated filling pressures, rising BUN/Creatinine, and hyponatremia
- Careful evaluation for advanced therapies is critical. Contraindications to transplant include fixed pulmonary hypertension, comorbidities limiting life expectancy, end-organ dysfunction not expected to improve following transplant and ongoing alcohol or substance abuse. LVAD evaluation requires assessment of RV function, left ventricular geometry, comorbidities and end-organ dysfunction as well as appropriate social support
- Early palliative care involvement both for symptom management and a patient-centered approach that includes advanced care planning is essential

Research Points

- Identifying which patients will benefit most from the two main types of durable advanced therapies (transplant or LVAD) remains difficult to determine and current prediction models are suboptimal. Risk scores to better define appropriate candidates for transplant versus LVAD are required.
- Renal dysfunction is a major cause of morbidity in heart failure and the optimal management of these patients in the context of advanced therapies remains unknown. Further strategies to determine reversibility of end-organ dysfunction are required.
- The optimal timing for advanced therapies is unknown with early intervention resulting in lack of benefit at the cost of increased risk while unnecessary delay may render a patient ineligible or run the risk of poor outcomes. Defining the ideal timing for intervention is a critical next step in the management of end-stage heart failure.

Figure 1.

Table 1

Causes of Heart Failure

Ischemia	Coronary Artery Disease Myocardial infarction Spontaneous Coronary Artery Dissection
Drugs & Toxins	Alcohol Cocaine Amphetamines Chemotherapeutics
Infectious	Lymphocytic myocarditis Giant Cell myocarditis
Metabolic	Thyrotoxicosis Anemia Nutritional Deficiencies (e.g. BeriBeri)
Infiltrative	Sarcoidosis Amyloidosis
Loading Condition Related	Hypertension Valvular Hypertrophic Cardiomyopathy Arteriovenous Malformations/fistulas
Arrhythmic	Tachycardia mediated Bradycardia mediated Chronic pacing Arrhythmogenic Right Ventricular Cardiomyopathy
Other	Familial (Genetic) Peripartum Cardiomyopathy Muscular Dystrophy Related

Table 2

Parameters associated with advanced HF

Symptoms and Exam findings	Clinical Course	Objective Measures
<ul style="list-style-type: none"> Dyspnea at rest or with ADLs (dressing, bathing) Severe exercise limitation (<1 block) Hypotension (SBP<90mmHg) Weight loss not due to other cause 	<ul style="list-style-type: none"> Recurrent (≥ 2) hospitalizations/ED visits in the past year Frequent ICD shocks Escalating diuretic requirements Intolerance of beta-blockers or ACE inhibitors 	<ul style="list-style-type: none"> Peak VO₂<12–14mL/kg/min Elevated cardiac filling pressures; PCWP>16 and/or RAP>12 6-MWT distance <300m (women, patients >75 years) Elevated BNP or NT-pro BNP Worsening renal function (rising BUN/Creatinine) Hyponatremia (Na<133mEq/L)

ADLS, activities of daily living; SBP, systolic blood pressure; ED, emergency department; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; 6-MWT, six-minute walk test; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal proBNP; BUN, blood urea nitrogen; Na, sodium