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ADVANCED THERAPIES FOR HEART FAILURE

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CONTENT

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ADVANCED THERAPIES FOR HEART FAILURE

ABSTRACT

Heart failure is a clinical syndrome that results when the heart is unable to provide sufficient blood flow to meet metabolic requirements or accommodate systemic venous return. This common condition affects over 5 million people in the United States at a cost of $10-38 billion per year. Heart failure results from injury to the myocardium from a variety of causes including ischemic heart disease, hypertension, and diabetes. Less common etiologies include cardiomyopathies, valvular disease, myocarditis, infections, systemic toxins, and cardiotoxic drugs. As the heart fails, patients develop symptoms which include dyspnea from pulmonary congestion, and peripheral edema and ascites from impaired venous return. Constitutional symptoms such as nausea, lack of appetite, and fatigue are also common. There are several compensatory mechanisms that occur as the failing heart attempts to maintain adequate function. These include increasing cardiac output via the Frank-Starling mechanism, increasing ventricular volume and wall thickness through ventricular remodeling, and maintaining tissue perfusion with augmented mean arterial pressure through activation of neurohormonal systems. Although initially beneficial in the early stages of heart failure, all of these compensatory mechanisms eventually lead to a vicious cycle of worsening heart failure. Treatment strategies have been developed based upon the understanding of these compensatory mechanisms. Medical therapy includes diuresis, suppression of the overactive neurohormonal systems, and augmentation of contractility. Surgical options include ventricular resynchronization therapy, surgical ventricular remodeling, ventricular assist device implantation, and heart transplantation. Despite significant understanding of the underlying pathophysiological mechanisms in heart failure, this disease causes significant morbidity and carries a 50% 5-year mortality.

CONCLUSIONS

Over the last 30 years, various pathways leading to the development and progression of heart failure have been identified and successfully targeted with effective therapies.

This has improved the quality of life and survival for millions of individuals with HFrEF, globally.

Hopefully, new treatments will offer further improvements and extend these successes to the treatment of HFpEF and other specific causes and phenotypes of HF.

New concepts of how HF should be defined combined with new analytical approaches using large data-sets will reshape its epidemiology and offer new therapeutic targets. However, old age rather than cardiac dysfunction may be the next great barrier to overcome.

KEYWORDS: heart failure, advanced therapy , palliative care

INTRODUCTION

Heart failure (HF) is a clinical syndrome caused by structural and functional defects in myocardium resulting in impairment of ventricular filling or the ejection of blood. The most common cause for HF is reduced left ventricular myocardial function; however, dysfunction of the pericardium, myocardium, endocardium, heart valves or great vessels alone or in combination is also associated with HF. Some of the major pathogenic mechanisms leading to HF are increased hemodynamic overload, ischemia-related dysfunction, ventricular remodeling, excessive neuro-humoral stimulation, abnormal myocyte calcium cycling, excessive or inadequate proliferation of the extracellular matrix, accelerated apoptosis and genetic mutations [1].

CLASSIFICATION OF HF

The New York Heart Association (NYHA) functional classification defines four functional :classes as

Class I: HF does not cause limitations to physical activity; ordinary physical activity does not .cause symptoms

Class II: HF causes slight limitations to physical activity; the patients are comfortable at rest, .but ordinary physical activity results in HF symptoms

Class III: HF causes marked limitations of physical activity; the patients are comfortable at .rest, but less than ordinary activity causes symptoms of HF

Class IV: HF patients are unable to carry on any physical activity without HF symptoms or have symptoms when at rest.

NEURO-ENDOCRINE INTERVENTIONS AUGMENTATION OF NATRIURETIC AND OTHER PEPTIDES:

sacubitril/valsartan

One of the key therapeutic successes for heart failure has been the inhibition of neuro-endocrine pathways with ACE-Is, ARBs, MRAs and beta-blockers. Recently, a new class of agents, angiotensin receptor neprilysin inhibitors (ARNI), has proved superior to ACE-Is for the treatment of HFrEF [1]. Neprilysin inhibitors retard the degradation of many peptides, including atrial (ANP) and B-type natriuretic peptides (BNP) and vasoactive intestinalpolypeptide, which have diuretic, vasodilator and inotropic properties [2, 3]. In the Comparison of Sacubitril–Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode (PIONEER-HF) trial,

initiation of sacubitril/valsartan for patients with either new-onset or chronic HFrEF (n = 881) during the in-hospital recovery phase after an acute decompensation was as safe as initiating enalapril, but led to a greater, and earlier (within 1 week), reduction in plasma concentrations of NT-proBNP, which was sustained until the end of 8 weeks follow-up [4]. A reduction in a composite of serious HF-related adverse clinical events was also observed [5]. However, about 20% of surviving patients discontinued treatment with either ACEi or ARNI and only 55% achieved guideline-recommended doses of the ARNI [4] . In the PRIME trial (n = 118), patients with HF, an LVEF < 50% and functional mitral regurgitation (MR) who were randomised to sacubitril/valsartan had a greater reduction in the effective regurgitant orifice area (EROA) compared with valsartan alone at 12 months follow-up [6]. Other trials are currently ongoing in specific populations with HFrEF, including those with symptoms at rest (NCT02816736), or an elevated pulmonary artery pressure (NCT02788656) or in Japan (NCT02468232). The Prospective Comparison of ARNI with ARB Global Outcomes in HF With Preserved Ejection Fraction (PARAGON; NCT01920711) is a randomised, double-blind, event-driven trial comparing the efficacy and safety of valsartan vs sacubitril/valsartan in patients with HFpEF that has enrolled 4822 patients (mean age 73 ± 8 years, median NT-proBNP 911 (interquartile range 464–1610) pg/mL, > 2/ 3 in sinus rhythm) [7]. The results should be reported later in 2019. PARALLAX (NCT03066804) is another large (> 2,000 patients) randomised, double-blind trial of patients with HFpEF, comparing sacubitril/valsartan with a control group (the investigator can chose whether this is an ACE-I, an ARB or neither, in which case patients assigned to the control group receive placebo); the effect on plasma NT-proBNP and exercise capacity after 24 weeks of treatment and safety are the main outcomes of interest. Concerns exist that the inhibition of neprilysin could interfere with breakdown of beta amyloid (βA) peptides, which might accumulate in the brain and contribute to the development of Alzheimer's disease. The PERSPECTIVE trial (NCT02884206) is currently recruiting ~ 500 patients with HF and LVEF > 40%, to investigate whether chronic administration of sacubitril/valsartan for 3 years leads to a decline in cognitive function when compared with valsartan alone.

VASODILATORS:

vericiguat and nitroxyl Nitric oxide (NO) activates soluble guanylate cyclase (sGC), causing an elevation of intracellular cyclic guanosine monophosphate (cGMP) in vascular and non-vascular tissues, such as the myocardium and kidney. In heart failure, production of NO is reduced and its degradation is increased, leading to an increase in systemic and pulmonary arteriolar and venous tone, thereby increasing the after-load and pre-load on the failing myocardium [8]. Vericiguat is an oral Sgc stimulator which increases cGMP production. Phase 2 trials showed that vericiguat is well tolerated in patients with HFrEF [9]. A large (~ 4,500 patients) phase 3 trial (VICTORIA; NCT02861534) is currently evaluating whether vericiguat improves morbidity and mortality compared with placebo in patients with chronic HFrEF [35]. Nitroxyl is a second-generation donor of nitric oxide that causes vasodilatation and may have inotropic effects, which are only partially mediated by an increase in cGMP [10].

A phase 2 trial (STAND-UP; NCT03016325) is currently evaluating the safety and efficacy (changes in NT-proBNP and symptoms) of 48-h infusion of nitroxyl in 310 patients admitted with decompensated HFrEF. Smaller mechanistic trials are investigating its effects on cardiac and renal function.

INOTROPIC AGENTS

Omecamtiv mecarbil, levosimendan, digoxin and recombinant human neuregulin-1 Omecamtiv mecarbil (OM) is a cardiac myosin activator that alters the kinetics of actin/myosin cross-bridges, prolonging the duration of the systole and, thus, stroke volume, without increasing ATP consumption [11]. Phase II trials showed that IV administration of OM in patients with acutely decompensated HFrEF had the expected haemodynamic effects but no clear clinical benefit [12]. In The Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure (COSMIC-HF) trial, oral OM given for 20 weeks was safe and reduced LV size and plasma concentrations of NT-proBNP levels; the latter effect persisted for 4 weeks after treatment withdrawal suggesting that long-term favourable structural remodelling had occurred [13]. The Phase II trial programme has repeatedly shown small increases in serum troponin concentrations, raising concerns about safety that, so far, appears unfounded. Increases in troponin appear unrelated to any clinical evidence of myocardial ischaemia or adverse outcomes. A large (n ~ 8,000) phase III trial of patients with chronic HFrEF (with 25% planned to be enrolled during a hospitalisation for an episode of decompensation) is nearing completion of enrolment and should report in 2021 (GALACTIC-HF; NCT02929329). Levosimendan, a vasodilator and calcium sensitiser, has been used to treat refractory HF in many countries despite two large neutral trials conducted in patients with acute HF and a large trial of an oral formulation in patients with chronic severe HF that showed reductions in NT-proBNP and an improvement in QoL but did not otherwise improve outcome [14, 15]. Recently, small trials have explored the effects of giving levosimendan intermittently to patients with chronic severe HFrEF and shown that this can reduce plasma concentrations of NT-proBNP [16]. Larger trials are now attempting to determine whether this strategy can improve symptoms, exercise capacity, morbidity and mortality in patients with HFrEF. Neuregulin-1 proteins are important for the development and function of cardiac myocytes. Small phase II studies reported that recombinant human neuregulin-1 improved haemodynamics and promoted reverse LV remodelling in patients with HFrEF [17, 18]. A phase III study is currently testing whether, compared to placebo, use of daily (for 10 days) IV infusions, followed by weekly boluses, of recombinant human neuregulin-1 is feasible, safe and effective in reducing mortality in Chinese patients with mild to moderate chronic HFrEF. Digoxin may be the oldest medicine still prescribed for heart failure, but controversies persist about its benefits. In the DIG trial, conducted before many current HF treatments were available, digoxin did not reduce mortality compared to placebo, although it did reduce HF hospitalisations by 28%. A retrospective analysis suggested that patients with serum concentrations of digoxin of 0.5–0.9 ng/mL were more likely to benefit [19, 20]. A prospective, randomised, placebo-controlled trial is testing whether lower doses of digoxin, guided by measurements of its plasma concentrations (0.5–0.9 ng/mL),

will reduce HF hospitalisations and cardiovascular death in ~ 1,000 symptomatic patients with chronic HF and a reduced or mid-range LVEF (< 50%) (NCT03783429).

TORASEMIDE, ACETAZOLAMIDE AND OTHER DIURETICS LOOP DIURETICS

are the most potent diuretic agents, and furosemide is the most widely used in patients with HF. However, other loop diuretics, such as bumetanide and torasemide, are either better absorbed or delivered more reliably to the renal tubule. Meta-analysis of small randomised trials and observational studies suggests that torasemide might be superior to furosemide, but no substantial randomised trial has yet compared these two agents [21_22]. TRANSFORM-HF (NCT03296813) is an ongoing, multi-centre, unblinded, trial that will randomise, prior to discharge, ~ 6000 patients admitted with decompensated heart failure to long-term treatment with oral torasemide or furosemide to investigate effects on morbidity and mortality. Other options for treating resistant congestion in patients HF exist, such as combining different classes of diuretics, but their safety and efficacy have been rarely tested in clinical trials [23]. Most of the sodium filtered by kidneys is reabsorbed in the proximal tubule of the nephron. Acetazolamide, a carbonic anhydrase inhibitor, should decrease the amount of sodium reabsorbed in the proximal nephron and enhance the distal effects of loop diuretics. The Acetazolamide in Decompensated heart failure with Volume OveRload (ADVOR) is a randomised, double-blind, placebocontrolled trial which will test whether combining acetazolamide with a loop diuretic is more successful in achieving decongestion in ~ 500 patients admitted with HF and signs of fluid overload [24].

SODIUM GLUCOSE CO-TRANSPORTER 2 INHIBITORS

Although not everyone would agree that it is the principal mechanism of action of sodium glucose co-transporter 2 inhibitors (SGLT2i), there is little doubt that diuresis contributes to their effects in HF. SGLT2i reduce glucose reabsorption in the proximal nephron, increasing delivery of glucose and sodium to the distal nephron and inducing an osmotic diuresis. Whether SGLT2i have additional metabolic effects on the heart and kidney by inhibiting carbonic anhydrase or increasing the availability of ketones as a metabolic substrate for the myocardium is uncertain [25]. Empagliflozin reduced allcause mortality and hospitalisation for heart failure in patients with type 2 diabetes mellitus (T2DM) and ischaemic heart disease (IHD) [26]. Trials of canagliflozin and dapagliflozin also suggested a reduction in hospitalisations for HF [27–28]; although the relative risk reduction was substantial, the absolute benefits were very small, creating uncertainty about whether they are clinically meaningful. Interestingly, the programme of phase III trials for HF has not required patients to have T2DM and has enrolled a broad range of patients with HFrEF and HFpEF as well as in-patients and out-patients. The first of these trials is likely to report in 2019 (DAPA-HF) [27].

CARDIAC TRANSPLANTATION

The only true "cure" for refractory or end-stage HFrEF is cardiac transplantation. The first heart transplant using a cadaveric donor was performed December 3, 1967 by Dr. Christiaan Barnard in Cape Town, South Africa.

This operation occurred one month before Dr. Norman Shumway performed the first case in the United States (US). The early years of transplantation were marked by difficulties balancing infection and rejection.Medical immunosuppression was greatly advanced after Cyclosporine A became available in 1983, resulting in fewer complications. At present, over 104,000 heart transplantations have been performed in more than 200 hospitals across the world, with an estimated rate of approximately 3,800 per year, over half of which are performed in the US [28]. Unfortunately, organ shortages chronically limit this therapy. Approximately 2,800 patients are listed for heart transplant annually in the US, but the yearly wait-list mortality approaches 15% . Thus, it has become paramount to choose transplant recipients judiciously, and to ensure that all other alternative therapies have been exhausted.

TABLE 1. INDICATIONS AND CONTRAINDICATIONS FOR REFERRAL AND CONSIDERATION OF ADVANCED HEART FAILURE THERAPIES (HEART TRANSPLANTATION, VENTRICULAR ASSIST DEVICE IMPLANTATION).

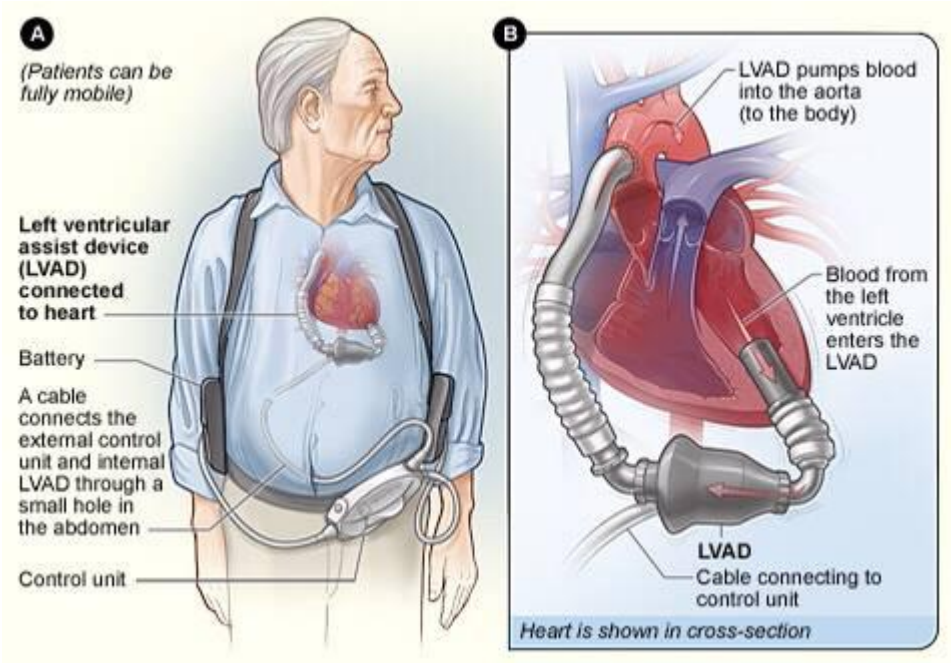
Indications	Contraindications
1. NYHA Class III-IV despite optimal medical and device therapy 2. 6-minute walk < 300 m (984 feet) and/or peak oxygen consumption < 12-14 cc/kg/min 3. Intolerance or withdrawal of evidence-based HF medications (e.g., beta-blockers, ACE-inhibitors) due to hypotension 4. Diuretic-refractory volume overload 5. Worsening renal function 6. Frequent acute HF hospitalizations not related to noncompliance 7. Need for intravenous inotrope 8. Refractory life-threatening ventricular arrhythmias or frequent ICD discharges 9. Refractory debilitating angina despite revascularization and symptom-oriented therapies	1. Noncompliance with medical regimen 2.Active substance abuse 3.Severe symptomatic cerebrovascular disease 4.Severe dysfunction of other organs (lung, kidney1, liver1, coagulopathy(5.Active infection 6.Active mental illness 7.Inadequate social support 8.Fixed, severe pulmonary hypertension 1,2 9.Morbid obesity (BMI > 35 kg/m2) 2 10.Age > 70 years 2 11.Recent or uncured malignancy 2 12.HIV 2 13.Hepatitis C 2 14.Abdominal aortic aneurysm 15.Inability to tolerate anticoagulation 3

VENTRICULAR ASSIST DEVICE THERAPY

Historically cardiac transplantation has been the only treatment for prolonging life in patients with advanced HFrEF. However, donor hearts remain a critically scarce resource and many end-stage HFrEF patients are transplant-ineligible, due to medical or psychosocial factors. MCS has now emerged as a treatment for enhancing quality-of-life and reducing mortality.

The origins of MCS date back to the 1950s with the early use of cardiopulmonary bypass for high-risk cardiac interventions [29]. In light of the obvious benefits of circulatory support in the operating room, these bypass machines soon were transitioned into the intensive care units where they were used to recover patients post-operatively and to buttress vital organ perfusion in individuals with refractory shock. Shortly thereafter, the National Institutes of Health established the Artificial Heart Program [30].

The ventricular assist device (VAD) has undergone substantial changes over the past decades. Beginning with Debakey's use of a pneumatic left ventricular assist device (LVAD) [31], innovations in design have resulted in devices that are smaller, more durable, and more efficient. Figure **2** highlights monumental events which have shaped the evolution of VAD therapy.



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