Congestive Heart Failure: Current Treatment and Therapies under Realm of Research

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Abstract The continuous increase in total congestive heart failure cases and the economic burden associated with it has led to the overwhelming demand for novel therapies. Quite a few drugs for heart failure have shown some promise in preclinical as well as early-phase clinical trials, but most of them were unsuccessful to show the real benefit in pivotal trials. Ivabradine and sacubitril/ valsartan are the new promising drugs to treat heart failure which has been approved recently by the United States Food and Drug Administration. Moreover, some of the newer agents under research offer the potential for noteworthy progress in addition to these drugs. Furthermore, Gene therapy and Stem cell therapy are the recent advances which are being explored and so far have proven to be useful as evidenced by clinical trials. Apart from synthetic molecules, there are also some natural agents such as L-arginine, Coenzyme Q10 etc. which aids in the management of congestive heart failure. In addition to the pharmacological treatment, non-pharmacological intervention also plays an essential role in management of congestive heart failure. To assess the true effectiveness of these attractive compounds future clinical trials with proper patient selection, optimal clinical endpoints and more appropriate study designs are mandatory.

Keywords Congestive Heart Failure, Pharmacological Treatment, Non-pharmacological Intervention, Gene Therapy, Stem Cell Therapy

1. Introduction

Congestive heart failure (CHF) is coupled with lack of ability of the heart to empty itself adequately, with the consequence that there is a high venous filling pressure and a decrease in the effective work done by the heart muscle.

There are a number of factors that, if severe, will produce congestive heart failure. These factors include

valvular obstruction or inadequacy, mechanical obstruction of the heart, as in pericardial disease; large intracardiac shunts which increase the load on ventricles; the presence of elevated pressure in the pulmonary or systemic circulation; inflammatory reactions in the heart muscle or lack of oxygen; and, also, certain metabolic disturbances, such as hyperthyroidism or hypothyroidism. Endpoint components of this syndrome such as a) Volume overload (congestion) b) and myocardial dysfunction (heart failure) are the main focus of drug therapies [1].

Before discussing the clinical pharmacotherapy of heart failure, it is useful to set up a pathophysiologic groundwork through which its treatment can be approached.

2. Brief Pathophysiology of CHF

Pump failure causes a decreased stroke volume/cardiac output (CO). In response to this, compensatory mechanisms kick in to increase CO. Sympathetic nervous system stimulation leads to release of epinephrine/nor-epinephrine causing increase in heart rate (HR), contractility and peripheral vasoconstriction (increase in afterload). Sometimes walls of heart thicken to provide more muscle mass for stronger contractions (myocardial hypertrophy). Hormonal response leads to decreased renal perfusion interpreted by juxtaglomerular apparatus as hypovolemia. Thus kidneys release renin, which stimulates conversion of angiotensin I to angiotensin II, which causes release of aldosterone and ultimately increase sodium (Na) and water retention (peripheral vasoconstriction).

CO may be restored to near-normal by compensatory mechanisms. But, if excessive the compensatory mechanisms can worsen heart failure. Vasoconstriction increases the resistance against which heart has to pump and may therefore reduce CO. Na and water retention increases the fluid volume which increases preload. Too much “stretch” will lead to decrease in strength of contraction and decreases CO [2], [3].

3. Objective

The article discusses about the conventional drugs used to treat congestive heart failure as well as the recent advances in the treatment. It also talks about the drugs which are recently approved by the US FDA for the management of Congestive Heart Failure. Benefit of Non-pharmacological management has been covered. The article will be helpful in shedding a light on natural compounds which can aid in the management of Congestive Heart Failure. There are certain drugs which are still under research and undergoing clinical trials. These drugs might evolve as new therapies in congestive heart failure treatment. Several clinical trials using gene as the potential treatment have also been done. Another emerging therapy for the management of congestive heart failure is Stem cell therapy. Authors have tried to summarize the above treatments in this review.

4. Methods

Literature search: The electronic databases of Ovid MEDLINE®, EMBASE®, PubMed®, and Scopus® were searched to identify relevant citations of published trials.

Selection of Studies: Randomized controlled trials (RCTs) fulfilling certain specified criteria were selected. Cohort studies, case series and case reports are excluded from the review owing to the high potential for bias in these study designs.

Studies published between 2005 and the present were included within the review article. The author and a review team screened 47 citations.

Key words used for searching were congestive heart failure, recent advances in heart failure treatment, gene therapy, stem cell therapy, nutraceuticals, device used in heart failure.

5. Current Pharmacological Treatment of CHF

Drug Classes Used to Treat CHF [4], [5], [6]:

- Cardiac glycosides Eg. Digitoxin
- Angiotensin converting enzyme inhibitors (ACE inhibitors) and A₁ Receptor Antagonists. Eg. Captopril
- Vasodilators Hydralazine, Nitrates
- Aldosterone Antagonists
- β Adrenergic Receptor Antagonists Beta-blockers
- Vasodilators
- Diuretics
 - (a) High Ceiling Loop Diuretic Eg. Furosemide
 - (b) Benzothiadiazide Diuretic Eg. Chlorthalidone
 - (c) Potassium Sparing Diuretics Eg. Spironolactone

- (d) Osmotic Diuretics Eg. Mannitol

Surgical Options

Left Ventricular Assist Devices (LVADs)

For mechanical circulatory support, certain patients with NYHA Class IV symptoms and end-stage heart failure are referred to a tertiary care center. Currently, LVADs are used as a destination therapy in patients ineligible for transplantation or as a bridge to cardiac transplantation in patients who are appropriate transplantation candidates. The inflow cannula of an LVAD is connected to the apex of the left ventricle and the device mechanically pumps the blood to the aorta via outflow cannula. Common and often life threatening complications following LVAD implantation are; infection, stroke, bleeding, coagulopathy and multisystem organ failure. Rotary continuous flow LVADs are associated with fewer complications and are more durable [7], [8].

Cardiac Transplantation

Cardiac transplantation is reserved for otherwise healthy patients who despite after optimal medical therapy have end-stage heart failure with severely impaired functional capacity. Patients with chronic medical co-morbidities, pulmonary hypertension, psychosocial contraindications, active infection or medical noncompliance are not considered for transplantation. Survival rate after cardiac transplantation is about 85% at 1 year, and approximately 13 years median life expectancy. Rejection, transplant coronary vasculopathy, infection and malignancy are the complications which limit survival. Patients are subjected to lifelong immunosuppression post cardiac transplantation to prevent rejection, which in turn renders them vulnerable to various opportunistic infections and malignancies [9].

6. Drugs Recently Approved by US Food and Drug Administration (FDA) for Treating Heart Failure

Sacubitril/Valsartan

Valsartan is a renin-angiotensin-aldosterone system (RAAS) blocker whereas sacubitril is a neprilysin inhibitor (ARNi). Neprilysin is an enzyme that degrades natriuretic peptides (NPs). Combination of valsartan with sacubitril has recently come into sight as a potentially superior treatment approach. Sacubitril/valsartan was approved by FDA in July 2015 for use in patients with chronic and stable but symptomatic HF and having LVEF of less than 40%. As NPs promote natriuresis, diuresis, and vasodilation, inhibition of neprilysin is considered to be the therapeutic target to work against the neurohormonal activation and also it complements RAAS inhibition. The

PARADIGM (Prospective Comparison of ARNi with ACE Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial provided strong evidence for superiority of the ARNi in patients with HF with reduced ejection fraction (HFrEF) [10], [11].

Sacubitril/Valsartan is a novel addition to the current hypertension armamentarium as it appears to be more efficacious in reducing blood pressure than currently available ACEi and ARBs possessing similar safety and tolerability profile. In addition it also has pleiotropic benefits like better Estimated Glomerular Filtration Rate (eGFR) progression, Glycated haemoglobin (HbA1c) reduction and a greater decrease in BP and serum creatinine levels [12]. In a study, Sacubitril/valsartan proved superior to enalapril in reducing the risk of CV death or HF hospitalization and all-cause death. Sacubitril/valsartan was generally well tolerated, with a similar safety profile to enalapril; renal dysfunction, hyperkalemia and cough were less common when compared with enalapril [13].

Ivabradine

Without affecting the myocardial contractility or relaxation, ventricular repolarization, or intracardiac conduction, Ivabradine works by reducing heart rate by inhibition of specific sinus node pacemaker *I_f* current. In Beautiful (Morbidity-Mortality Evaluation of the *I_f* inhibitor Ivabradine in Patients with Coronary Artery Disease and Left Ventricular Systolic Dysfunction) trial ivabradine revealed a clear benefit with respect to the secondary endpoints of admission to a hospital for a fatal or non-fatal myocardial infarction and coronary revascularization [14].

In SHIFT (Systolic HF Treatment with *I_f* Inhibitor Ivabradine) trial, Ivabradine significantly reduced the primary endpoint of a composite of cardiovascular death or hospital admission for worsening HF and deaths due to HF. Ivabradine is clearly indicated in patients with symptomatic systolic LV dysfunction, in sinus rhythm and an heart rate of at least 75 beats per minute despite a maximum tolerated beta-blocker therapy [15].

However, Current therapies are not adequately effective at improving health and preventing deaths. Thus scientists are exploring newer molecules which can be useful in prophylaxis or treatment of heart failure.

7. Treatments in Realm of Research with No Firm Recommendations

Bromodomain and Extra Terminal Domain (BET) Proteins Inhibitors

HF may be provoked by the activation of a large set of genes that thickens the walls of the heart and develop scar

tissue which can be correlated with the organ's inability to pump blood normally. A study published by in the journal *Cell* reveals that bromodomain and extra terminal domain (BET) proteins plays a key role in activating genes which contribute to HF. BET proteins functions as a critical coactivator of pathologic gene transactivation during cardiomyocyte hypertrophy [16].

BET inhibitor called JQ1 protect against heart-wall thickening, the formation of scar tissue, and pump failure [17] thus, showing potential promise in treating heart failure. BET inhibitors needs to be explored in preclinical as well as in clinical trials.

Apelin

A synthetic peptide is developed by researchers at the University of Alberta that could be the first in a new class of drugs to treat heart disease. Researchers found that a deficiency in the peptide apelin is associated with HF. They developed synthetic apelin that promotes blood vessel growth. Synthetic form of apelin is far more potent and stable than the naturally occurring peptide, making drug therapies possible. The research team studied deficiency of apelin through Human Explanted Heart Program (HEHP) found that hearts from patients who suffered heart attacks were deficient in apelin, which is needed for angiogenesis [18].

In vivo models with apelin have shown significant increases in LV stroke volume and contractility in failing hearts. Apelin supplementation in rats demonstrated improvement in the performance of the failing myocardium and also attenuated the development of HF secondary to LV pressure overload [19]. Currently researchers are studying apelin for in-depth knowledge and treatment potential of the molecule.

Patiromer

It is evidenced that hyperkalemia is associated with the use of RAAS inhibitors in patients with HF, especially in with chronic kidney disease (CKD) patients. Moreover, hyperkalemia has become a major limiting factor to titrate RAAS inhibitors in patients who are most likely to benefit from treatment [20]. Caution is exercised when using angiotensin-receptor blockers and ACE inhibitors in patients at risk for hyperkalemia. In patients receiving some combination of an ACE inhibitor, an angiotensin-receptor blocker, and an aldosterone-receptor blocker, discontinuation of one drug may also be effective in lowering the serum potassium concentration. Such drugs may need to be avoided if the serum potassium concentration is 5.6 mmol per liter or higher despite the precautions described above. Particular attention should be given to patients with underlying disturbances of cardiac conduction, since even mild degrees of hyperkalemia can precipitate heart block [21].

Thus, agents able to control the plasma concentration of potassium and at the same time maintaining the use of RAAS inhibitors are looked-for. Patiromer calcium, which is a novel potassium absorbent is designed to increase potassium loss via the gastrointestinal tract have showed efficacy and safety in recent trials. The OPAL-HK trial (A Two-Part, Single-Blind, Phase 3 Study Evaluating the Efficacy and Safety of Patiromer for the Treatment of Hyperkalemia) evaluated the efficacy and safety of patiromer in 243 CKD patients taking RAAS inhibitors and having high levels of serum potassium. After the initial 4 weeks of active treatment, mean reduction in plasma potassium levels was 1.0 mEq/l. [20], [22].

Serelaxin

Serelaxin is a recombinant form of naturally occurring hormone relaxin, which is produced by the corpus luteum and placenta in pregnancy and also by the vasculature and failing myocardium. Relaxin by interacting with a G protein-coupled receptor leads to increase in cyclic adenosine monophosphate (cAMP) and increases NO production. Due to ability of relaxin to increase renal perfusion as well as having potent vasodilator properties, it has become interesting potential therapy for acute HF [23].

The RELAX-AHF trial (Relaxin in Acute Heart Failure) was an RCT in which 1,161 acute decompensated heart failure (ADHF) patients were enrolled. Patients were randomly allocated to receive serelaxin or placebo within 16 hours from presentation. Serelaxin shortened the length of hospital stay, significantly improved dyspnea and lessened the incidence of worsening HF as compared with placebo. Even though relaxin has shown success in improving the clinical course of patients during the initial hospitalization with an acceptable safety profile, a larger trial is ongoing to expectantly validate whether this drug could certainly provide long-term mortality benefit [23], [24]

Gene Therapy

Gene therapy is a technique that uses genes to treat or prevent disease. Instead of using drugs or surgery this technique allows the doctors to treat a disorder by inserting a gene into a patient's cells. Researchers are testing several approaches to gene therapy, including:

- Replacing a mutated gene that causes disease with a healthy copy of the gene.
- Inactivating, or "knocking out," a mutated gene that is functioning improperly.
- Introducing a new gene into the body to help fight a disease.

SER Ca²⁺ gene

Calcium handling ; influx of Ca²⁺ via L-type Ca²⁺

channels which opens when there is depolarization of action potential, indicates the contraction of cardiac muscles. Sarcoplasmic reticulum activated by Ca²⁺ leads to contraction which is result of Ca²⁺ binding to troponin c, which relieves actin-myosin interaction constraints. In heart failure, decreased expression of SER Ca²⁺ causes impairment of SR. There is a high diastolic and low systolic Ca²⁺ level when SER Ca²⁺ is impaired. Studies have shown that by increasing SER Ca²⁺ expression by viral transduction of SER Ca²⁺ transgene, heart failure can be treated [25].

In 2007, a human clinical trial sponsored by Celadon Corporation in which, (CUPID NCT00454818) a transgene was transferred via AAV1 vector by percutaneous intracoronary infusion. In this trial significant clinical improvement of cardiac remodeling and heart failure symptoms was reported [25], [26], [27]

Apart from SER Ca²⁺, calcium cycling proteins are also potential targets in heart failure.

Protein Phosphatase 1

A level of Protein phosphatase 1 (PP1) is increased in patients with heart failure. PP1 is associated with dephosphorylation of phospholamban (PLN). PLN comprises of 52 amino acids and is a small protein. Phosphorylated PLN has inhibitory effect on SERCA2. Thus, it is a prominent regulator of myocardial contractility. Inhibition of PP1 can improve cardiac contractility [28]. A PP1 inhibitor, Carfostin which contains active form of protein phosphatase 1 inhibitor protein has been developed by Nanocar therapeutics. Carfostin has shown promise in preclinical trials; in a study carried out by researchers at Mount Sinai, 13 pigs with severe heart failure induced by mitral regurgitation treated: 6 with Carfostin and 7 with placebo (saline) solution. The results demonstrated in the animal model that the gene therapy was safe and significantly reversed heart failure by 25 percent in the left ventricle and by 20 percent in the left atrium. The treatment group also showed a ten percent decrease in heart enlargement, a common symptom of heart disease [29]. Carfostin will soon undergo clinical trials.

Adenylyl Cyclase 6

Adenylyl cyclase 6 (AC 6) helps in β -adrenergic enhancement of heart contraction. It does this by converting adenosine tri phosphate (ATP) to CAMP and protein kinase A is activated. Phospholamban is phosphorylated by PKA and enhances SER Ca²⁺ activity. In heart failure AC 6 is reduced, thus activity of SER Ca²⁺ is reduced. Symptoms of heart failure are alleviated by viral delivery of AC 6 transgene as a result of increase SER Ca²⁺ function and phosphorylation of PLN [30].

Small Ubiquitine like Modifier

Small ubiquitine like modifier (sumo 1) is a key factor in

cardiac function, since it helps regulate calcium homeostasis in the mitochondria of heart cells. SUMO 1 is associated with another important cardiac protein called sarco/endoplasmic reticulum Ca^{2+} ATPase, or SERCA is a transmembrane protein located in the sarcoplasmic reticulum of cardiac cells. Its main function is to govern the discharge and uptake of intracellular calcium between the cytosol and the lumen of the Sarcoplasmic reticulum. Calcium is crucial factor for the development of cardiac myocyte contraction and relaxation. Thus, managing of intracellular calcium homeostasis by SER Ca^{2+} is critical for overall cardiac performance [31].

Gene Delivery Methods

A. Direct intramyocardial delivery

B. Transvascular intracoronary ante grade and retrograde delivery.

Most widely used viruses for gene delivery to heart are recombinant adeno associated virus (AAVs). They are selective for cardiomyocytes, also immunogenicity and rates of insertional mutagenesis is less. But their potential therapeutic effect and usage is limited due to restricted packaging capacity and inability to evade neutralizing antibodies. Strategies are going on to overcome these issues. In cardiomyocytes, cell specific promoters are useful to enhance their transgene expression. Virus can easily cross capillary endothelium; therefore intravascular delivery technique of virus is quite effective, although it is least invasive. Direct and indirect intracoronary injections are preferred to avoid post IV systemic neutralization, non-cardiac tissue transduction and subsequent toxicity. Recombinant vectors do not integrate with genome, thus follow up injections are necessary [28].

Stem Cell Therapy

Stem cells are undifferentiated cells that can differentiate into specialized cell types.

Stem cells are of from different types:

- Embryonic stem cells
- Induced pluripotent stem cells
- Skeletal myoblasts
- Bone marrow-derived stem cells
- Adipose-derived mesenchymal stem cells
- Cardiac stem cells
- Endometrial mesenchymal stem cells

Possible mechanisms of recovery include:

- Generation of heart muscle cells
- Stimulation of growth of new blood vessels to repopulate damaged heart tissue
- Secretion of growth factors
- Assistance via some other mechanism

Stem cell transplantation is a complex process that involves several steps. Autologous and allogeneic stem cell

transplants share similar process. However, in the case of autologous transplants, the stem cells of patients are collected and stored (frozen) until needed whereas in allogeneic transplants, stem cell donors usually undergo the collection procedure just before the transplant will be performed [32].

Delivery Methods for Cell Therapy in Heart Failure

- Intramyocardial
- Intravenous
- Epicardial Patches
- Retrograde

There are number of clinical trials performed using stem cell therapy and with different end points. In most of the studies, endpoints selected were LVEF, left ventricular end-systolic volume (LVESV), QOL, serious adverse event [33].

8. Some of the Natural Compounds Which Can Aid in the Treatment of Congestive Heart Failure

L-arginine Amino Acids

L-arginine improves blood flow to the heart by stimulating endothelial cell releasing factor (ECRF), thereby preventing formation of plaque in the arteries. L-arginine is a precursor of nitric oxide (NO); a compound which acts as a vasodilator. Dysfunction of the "L-arginine-nitric oxide" pathway in heart failure (HF) leads to reduced blood flow at rest and during exercise limiting the exercise capacity of chronic heart failure patients. In a 6 week study, patients with chronic stable heart failure who took L-arginine had a significant decrease in their average HR during exercise and the recovery period [34]. In another study, L-arginine appeared to help correct the abnormal functioning of blood vessels seen in chronic HF. L-arginine supplementation prolongs duration of exercise in CHF. Oral supplementation of L-arginine prolongs exercise duration in patients with chronic stable congestive heart failure, which may be due to peripheral vasodilatation induced by NO [35].

Hawthorn Extract

Hawthorn extract is a popular herbal medicinal product in the United States and also in European countries like Germany where it is a prescription medicine. Preparations usually contain extract derived from *Crataegus monogyna* or *Crataegus laevigata*. Clinical studies have reported an increase in LVEF, exercise tolerance and improvement in heart failure-related symptoms. The use of extracts of hawthorn leaf with flower is approved by German

Commission E for patients with New York Heart Association (NYHA) class II symptoms [36].

Coenzyme Q10

Coenzyme Q10 (CoQ10) is present naturally in the body. It works as an electron carrier in the mitochondria to produce energy and is also a powerful antioxidant [37]. In the heart muscle of patients with HF, CoQ10 levels are decreased and the deficiency becomes more pronounced when the severity of HF get worsen [38]. Cholesterol lowering drugs statins used in patients with HF also block the synthesis of CoQ10, which further decreases its levels in the body [39]. In several double blind controlled trials CoQ10 was able to improve symptoms, quality of life (QOL) and functional capacity in patients with heart failure without any side effects [38]. CoQ10 blocks the vicious metabolic cycle in chronic heart failure. CoQ10 is present in food, including plants and fish, but levels are not enough to make an impact on HF. It is the first drug to improve heart failure related deaths in over a decade [40].

9. Nonpharmacological Treatment of Congestive Heart Failure

Damage to the heart muscle can cause changes in the electrical system of the heart and thus lower the heart beats. There are different types of devices that can be used in the treatment of heart failure to correct an abnormal heartbeat.

Pacemakers

The traditional pacemaker consists of two parts: lead wires and a pulse generator, which houses a battery and a tiny computer. The lead wires act as heart's electrical activity sensor, and when the computer detects that the heart rhythm is off, it sends electrical impulses to the heart muscle to correct its rate. Pacemakers are generally used to treat heart rhythms that are very slow. But they are also beneficial in treating fast rhythms or to increase the heart rate in response to changes in the patient's activity level [41].

Biventricular Pacemakers (Cardiac Resynchronization Therapy)

In the normal heart, the heartbeat arise from specialized cells in the wall of the right atrium and spreads through the atria, causing them to squeeze blood into the ventricles, which then contract and pumps blood to the rest of the body. A condition known as dyssynchrony, in which the right and left ventricles often fail to pump together, is often seen in patients with heart failure. When this occurs, the heart has less time to fill with blood and is incapable to pump enough blood out into the body, which ultimately worsens the degree of heart failure. Biventricular pacemakers are

devices that use an extra lead wire to sense atrial contractions and send an electrical impulse to the two ventricles so that they contract at the same time. Cardiac resynchronization therapy (CRT) can improve symptoms of heart failure, reduce hospitalizations, increase patient's exercise tolerance and lengthen life [42].

To be eligible for a CRT, patients must be suffering from severe or moderately severe heart failure symptoms despite optimal medical therapy have QRS duration of minimum 135 milliseconds on the ECG and a LV ejection fraction of less than 35%. The patient should also be aware that the procedure of implantation may be technically challenging [42], [43].

Internal Cardioverter Defibrillator (ICD)

Patients with heart failure are at risk for life-threatening arrhythmias, such as ventricular fibrillation. This particularly holds true of patients who have survived sudden cardiac arrest, have an ejection fraction of less than 35 percent, or have a history of a fast ventricular arrhythmia. The ICD senses electrical activity and sends a shock to the heart if it detects a dangerous heart rhythm. Implantable cardiac defibrillators lessen the risk of death from sudden cardiac arrest in patients with heart failure. ICD can be considered as an "emergency room" inside your heart. If heart develops a fatal arrhythmia, the ICD will deliver a shock sometimes several, if required to restore a normal heart rhythm [44], [45].

Continuous Positive Airway Pressure

Additional novel approaches are required to improve the prognosis of CHF. Use of continuous positive airway pressure (CPAP) is one of the promising approaches. When applied via nasal mask, CPAP provides a noninvasive mechanical aid to the failing heart as it increases intrathoracic pressure and also assist in augmenting stroke volume and CO [21]. CPAP by decreasing LV transmural pressures during diastole and systole reduces left ventricular preload and afterload. In doing so, CPAP improves the mechanical efficiency of the failing heart and helps to reduce mitral regurgitation, possibly through reverse ventricular remodeling [46], [47]. Positive pressure ventilation is class III recommendation.

10. Discussion & Conclusions

Heart failure with a high rate of morbidity and mortality is a major health issue. Thus, there is a substantial need for novel approaches to avert the progression of heart failure. Until now, heart failure was seen as a grave and incurable disease. However, advancement in the treatment era such as gene therapy and stem cell therapy approach have offered the promise of a valuable therapy. Time will tell whether a single target approach is sufficient to restore

heart function and prevent deterioration or whether multiple gene targets are needed along with stem cell therapy to eventually replace the injured myocardium. Substantial progress in that direction has been made in the last few years. Great advances in understanding the pathophysiology of HF and their application to further improvements of patient care are within reach. Well-designed, large-scale, randomized clinical studies with objective end points will help to completely realize the therapeutic potential of advanced therapies for treating CHF.

Limitations: There is no talk of classification-based therapy as well as multiple well tried and approved therapies do not find mention in the paper. As it is a comprehensive review which includes established as well as emerging therapies for CHF, authors have not provided algorithm for the treatment.

11. Author's Contribution

Amogh R. Lotankar: Reviewed the literature, manuscript preparation and critical revision of the manuscript.

Altamash J. Momin: Collected data and review of literature and helped in preparing first draft of manuscript.

12. Conflict of Interest

None

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