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REVIEW ARTICLE

Recently Approved and Under Investigation Drugs for Treating Patients with Heart Failure

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Abstract: Heart Failure (HF) represents a leading cause of morbidity and mortality worldwide. Despite the recent advances in the treatment of this condition, patients´ prognosis remains unfavorable in most cases. Sacubitril/valsartan and ivabradine have been recently approved to improve clinical outcomes in patients with HF with reduced ejection fraction. Drugs under investigation for treating patients with HF encompass many novel mechanisms including vasoactive peptides, blocking inflammatory-mediators, natriuretic peptides, selective non-steroidal mineralocorticoid-receptor antagonists, myocardial β3 adrenoreceptor agonists, inhibiting the cytochrome C/cardiolipin peroxidase complex, neuregulin-1/ErbB signaling and inhibiting late inward sodium current. The aim of this manuscript is to review the main drugs under investigation for the treatment of patients with HF and give perspectives for their implementation into clinical practice.

Keywords: Heart failure, heart failure reduced ejection fraction, heart failure preserved ejection fraction, heart failure treatment, heart failure management, drugs for HF.

1. INTRODUCTION

Heart Failure (HF) is a composite clinical and neurohormonal syndrome, characterized by symptoms and signs of congestion and poor tissue perfusion. It is associated with abnormal systolic and/or diastolic cardiac function. HF is a multifactorial syndrome, and its prevalence is increasing worldwide [1, 2]. Data from the United States revealed an estimated 6.2 million Americans more than 20 years of age suffer from HF. This represents an increase of about one million patients with this condition over the last decade. Current projections estimate an increase of about 46% between 2012 and 2030 [3].

Over the last decades, a group of drugs has shown to reduce mortality or relieve symptoms and hospitalization in patients with HF. Both the American Heart Association/American College of Cardiology (AHA/ACC) and the European Society of Cardiology (ESC) have defined the first line of treatment for HF patients with reduced ejection fraction to include angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, carvedilol, bisoprolol and metoprolol succinate and aldosterone antagonists. Additional therapies include sacubitril/valsartan, ivabradine, cardiac resynchronization therapy, diuretics, digoxin, hydralazine/isosorbide dinitrate, left ventricular assistance devices and cardiac transplantation. In the case of patients with HF with preserved and mid-range ejection fraction, there are no evidence-based treatments for reducing mortality [4, 5].

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Despite the recent advances in the treatment of patients with HF, both hospitalizations and mortality are very common in this condition and impair the prognosis of patients [3]. This represents a health problem in the majority of developed and non-developed countries. On the other hand, several studies have demonstrated that the majority of costs in the management of HF patients are attributable to direct medical costs [6]. In this setting, new drugs should have a clinically relevant incremental effect compared to the current state of the art on hard clinical endpoints in patients with HF. Presently, a large number of new drugs are under investigation and may be an alternative for HF patients in the near future [2] (Table **1**), which encompasses several pathophysiological mechanisms (Table **2**). An example of years of investigation in this field is the recent approbation by the AHA/ACC and the ESC of sacubitril/valsartan for the treatment of symptomatic HF with reduced ejection fraction patients [4, 5].

Due to the importance for the medical community to know these novel treatments, in this manuscript, we review the main drugs (approved or under investigation) for the treatment of patients with HF and give perspectives for their implementation into clinical practice.

2. RECENT APPROVED DRUGS FOR HF TREATMENT

2.1 Sacubitril/Valsartan

For many years, angiotensin-converting enzyme inhibitors have been considered a first-line treatment in patients

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Table 1. Some randomized controlled trial on new HF drugs.

Drug	Authors	Study Characteristics	Main patients Characteristic at Baseline	Main Conclusions
Apelin	Barnes GD *et al.* [27]	Forty eight healthy patients and 12 HrEF patients	Age: 64 ± 3 years** Male sex: 75% LVEF: 19 ± 2% Ischemic cardiomyopathy: 75%	Apelin increased cardiac index and reduced mean arterial pressure and peripheral vascular resistance index
Anakira	Van Tassell BW *et al.* [32]	Sixty patients with decompensated HFrEF were randomized to receive anakinra or placebo. Patients were evaluated at 2 and 12 weeks	Age Anakinra: 60 (49-64) Placebo: 54 (49-66) Male sex Anakinra: 67% Placebo: 80% Ischemic cardiomyopathy Anakinra: 47% Placebo: 20% LVEF Anakinra: 24.6 (20.2-33.8) Placebo: 32.5 (21.8-39.0)	Anakinra improved oxygen consumption after 12 weeks of treatment, but no changes were seen in the first 2 weeks
	Van Tassell BW *et al.* [33]	Thirty-one patients with HFpEF and high levels of CRP were randomized to receive anakinra or placebo for 12 weeks	Age Anakinra: 54 (45-61) Placebo: 58 (51-64) Male sex Anakinra: 35% Placebo: 37% Ischemic cardiomyopathy Anakinra: 10% Placebo: 12.5% LVEF Anakinra: 60 (58-63) Placebo: 57 (50-62) E/E´ Anakinra: 9.8 (8.6-14.6) Placebo: 11.1 (10.2-13.4)	No changes in oxygen consumption after 12 weeks of anakinra administration was seen. CRP and NT-proBNP levels were lower after 4 weeks of treatment
Cenderitide	Kawakami R *et al.* [36]	Eighteen stable HF patients, 12 were randomized to cenderitide and 6 to placebo	Age: 63.2 ± 14.0 years Male: 88.9%, LVEF: 28.5 ± 10.7%*	Cenderitide was safe and well-tolerated. No changes in blood pressure was recorded
Finerenone	Filippatos G *et al.* [39]	One thousand sixty-six patients were randomized to receive oral, once-daily finerenone or eplerenone with a follow-up of 90 days	Age: 71.2 ± 10.1 years Male: 77.3% HTN: 73.5%, IHD: 64.4% LVEF: 29.1 ± 7.6%*	The percentage of individuals with a decrease of > 30% in plasma NT-proBNP was similar in both groups with a good safety profile
Mirabegron	Bundgaard H *et al.* [42]	Seventy HF patients with NYHA class II-III and LVEF < 40% were randomized to receive mirabegron or placebo for 6 month	Age Mirabegron: 62 ± 12 years Placebo: 56 ± 12 Female sex Mirabegron: 11% Placebo: 11 % LVEF by CT Mirabegron: 40 ± 11% Placebo: 38 ± 17%	Changes in LVEF were not significantly different between both groups. Patients with severe HF had higher improvement in LVEF

(Table 1) Contd…

Drug	Authors	Study Characteristics	Main patients Characteristic at Baseline	Main Conclusions
Elami-pretide	Daubert MA *et al.* [50]	Twenty four patients with HFrEF were randomized to a single4-hour infusion of elamipretide. Sample was divided into 3 successive ascending-dose cohorts and controls	Age: 62 ± 10 years Male: 78% LVEF: 29% Ischemic cardiomyopathy: 77%*	In the highest dose group, a significant decrease in left ventricular end-diastolic volume and end-systolic volume occurred. No serious adverse events were reported
Neuregulin	Gao R, *et al.* [55]	Forty four chronic HFrEF were randomized to receive recombinant neuregulin-1 at different doses or placebo. Patients were followed-up by 90 days	Age Neuregulin (0,6 ug/kg): 39 ± 14.5 years Placebo: 43 ± 10.0 Male sex Neuregulin (0,6 ug/kg): 91% Placebo: 100% NYHA functional class Neuregulin (0,6 ug/kg): 18% Placebo: 36%	Recombinant neuregulin-1 decreased end diastolic and systolic volumes compared with pre-treatment

Abbreviations: CRP: C-reactive protein, CT: computed tomography, HFpEF: Heart failure with preserved ejection fraction, HFrEF: Heart failure with reduced ejection fraction, HTN: Hypertension, IHD: Ischemic heart disease, NT-proBNP: N-terminal pro-brain natriuretic peptide, NYHA: New York Heart Association, LVEF: Left ventricular ejection fraction.
Note: *Characteristics refer to whole population in the study.
** Characteristics refers to HF patients in the study.

Table 2. Some pathways under investigation for new HF drugs.

Apelin
Interleukin-1b receptor antagonists
Atrial natriuretic peptides
Mineralocorticoid receptor antagonists
β3 agonists
Mitochondrial targeting peptide
Neuregulin-1
Cardiac ion channels modulator

with HF with reduced ejection fraction [7]. In patients with adverse side effects, angiotensin receptor blockers represent an alternative [8]. Both pharmacological groups, in combination with beta-blockers and antagonist mineralocorticoid receptors, reduce the risk of death in these patients [4, 5]. Experimental studies performed at the end of the last century demonstrated that simultaneous inhibition of neprilysin, a neutral endopeptidase that degrades natriuretic peptides, bradykinin and adrenomedullin, has beneficial effects on HF patients [9].

The PARADIGM study was a double-blind trial that assigned 8,442 patients with HF and an ejection fraction of 40% or less to receive either sacubitril/valsartan (LCZ696) or enalapril in addition to currently recommended therapy. The aim of this study was to demonstrate the effectiveness of sacubitril/valsartan for reducing cardiac death and hospitalizations in these patients. After a median follow-up of 27 months, the study was stopped early because the benefits with LCZ696 were clearly observed. The main finding of this trial was a reduction in death from cardiovascular causes in the LCZ696 compared with the in the LCZ696 compared with the enalapril group (HR: 0.80; 95% CI: 0.71-0.89; $p < 0.001$). As compared with enalapril, LCZ696 also reduced the risk of hospitalization for HF by 21% ($p < 0.001$) and decreased the symptoms and physical limitations of HF ($p = 0.001$). The main side effects were higher incidence of hypotension and angioedema in the LCZ696 group (14.0% *vs*. 9.2%; $p = 0.001$) and (0.2% *vs*. 0.1%; $p = 0.19$), respectively [10].

Many questions emerged in the medical community after PARADIGM-HF results were reported. For this reason, several post hoc analyses have been conducted and the main outcomes show that sacubitril/valsartan is an effective and safe choice for the treatment of patients with HF with reduced ejection fraction. Solomon *et al.*, evaluated the influence of ejection fraction on clinical outcomes and the effectiveness of sacubitril/valsartan compared to enalapril. The risk of all outcomes increased with decreasing left ventricular ejection fraction. Each 5-point reduction in left ventricular ejection fraction was associated with a 9% increased risk of cardiovascular death or HF hospitalization (HR: 1.09; 95% CI: 1.05 - 1.13; $p < 0.001$). Sacubitril/valsartan was effective across all left ventricular ejection fraction spectrum with no evidence of effect modification for the effectiveness of this drug by left ventricular ejection fraction [11]. Another analysis of PARADIGM-HF examined outcomes and effects of sacubitril/valsartan according to etiology (nonischemic *vs*. ischemic) in HF with reduced ejection fraction. Adjusted outcomes were similar across etiologic categories, as was the benefit of sacubitril/valsartan over enalapril [12]. Another secondary analysis of the PARADIGM-HF trial examined the effect of neprilysin inhibition on renal function in patients with type 2 diabetes and chronic HF. In patients in whom the renin-angiotensin system is already maximally blocked, the addition of neprilysin inhibition attenuates the effect of diabetes to accelerate the deterioration of renal function that occurs in patients with chronic HF [13]. Although PARADIGM-HF is one of the most transcendental

studies in the treatment of HF with reduced ejection fraction in the last decades, it has several limitations that should be carefully evaluated and interpreted in further analysis. Some limitations included the use of lower doses of enalapril than approved by current HF guidelines, while valsartan was given as maximal doses. The comparison of drug A + B *vs*. drug C was unique among all studies used to evaluate and approve cardiovascular drugs over the last decades and limitations in the patient's selection with few hospitalized patients, not enough New York Heart Association class IV and too young patients [14, 15].

In the PIONEER-HF trial, values of N-terminal proB-type Natriuretic Peptide (NT-proBNP) were lower in acute decompensated HF patients receiving sacubitril/valsartan compared to enalapril [16]. The use of sacubitril/valsartan in this setting was supported by the TRANSITION trial. In this study, sacubitril/valsartan initiation either in the hospital or shortly after discharge in acute decompensated HF patients was feasible and only 7.3% and 4.9% of patients discontinued its use due to adverse side effects in pre- and post-discharge groups respectively [17]. Sacubitril/valsartan has been found to be a cost-effective treatment for HF patients with reduced ejection fraction compared to other HF drugs, such as enalapril and angiotensin receptor blockers [18]. Another possible benefit of sacubitril/valsartan has been explored. Gonçalves *et al.*, evaluated 35 patients with HF with reduced ejection fraction who started sacubitril/valsartan treatment. Electrocardiographic and echocardiographic parameters were evaluated. After six months of follow-up, QTc interval (451.9 *vs*. 426.0 ms; $p < 0.001$), QRS duration (125.1 *vs*. 120.8 ms; $p = 0.033$) and mechanical dispersion index (88.4 *vs*. 78.1 ms; $p = 0.036$) were significantly reduced. These findings could explain possible antiarrhythmic properties of sacubitril/valsartan and a reduced risk for sudden cardiac death [19]. Pathophysiological mechanisms, which may explain these positive findings, include a reduction in cardiac fibrosis and beneficial cardiac remodeling seen in previous studies [20].

2.2. Ivabradine

Ivabradine has emerged as a new drug for treating patients with HF with reduced ejection fraction. International heart societies recommend ivabradine for reducing HF hospitalizations and/or cardiovascular death in symptomatic patients with HF with reduced ejection fraction (left ventricular ejection fraction $\leqslant$ 35%), New York Heart Association functional class II-IV and in sinus rhythm with resting heart rate of, at least, 70 beats per minute, in spite of treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers and aldosterone antagonists. Ivabradine is an If ion current inhibitor that selectively inhibits the pacemaker activity of the sinoatrial node. This drug reduces heart rate by a prolongation of the spontaneous phase of diastolic depolarization. Mechanisms that explain the benefits of ivabradine in this condition are diverse and include heart rate reduction, sympathetic system modulation and concomitant association with other drugs. Ivabradine has also demonstrated to be useful for symptom relief in patients with stable ischemic heart disease [21, 22].

The BEAUTIFUL trial (Morbidity-Mortality Evaluation of the If Inhibitor Ivabradine in Patients with Coronary Artery Disease and Left-ventricular Dysfunction) was the first randomized controlled study that evaluated the efficacy of ivabradine in patients with coronary artery disease and HF with reduced ejection fraction. 10,917 patients were randomized to receive ivabradine or placebo and were followed for a median of 19 months. At baseline, their mean age was 65 years, 83% were male, 88% had a previous myocardial infarction and 37% had diabetes. All patients were under treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and beta-blockers. Patients were stable for angina and HF symptoms for, at least, three months. The primary endpoint was a composite of cardiovascular death, admission for HF and myocardial infarction. There was no difference in the primary endpoint between both groups (HR: 1.00, 95% CI: 0,91-1.10; $p = 0.94$). A slight benefit of ivabradine use was seen in patients with the highest resting heart rate [23]. Although BEAUTIFUL was not a pure HF trial, it demonstrated that in patients with coronary artery disease and left ventricular dysfunction with resting heart rate over 70 beats per minute, the use of ivabradine reduces the incidence of hospitalizations due to fatal and non-fatal myocardial infarction and myocardial revascularization.

After these outcomes, a new randomized controlled trial was developed. The SHIFT (Systolic Heart Failure Treatment with the If Inhibitor Ivabradine Trial) trial evaluated ivabradine use in 6,558 patients with symptomatic chronic HF and left ventricular ejection fraction $\leqslant$ 35%. Patients were taking guideline-based therapy for HF and stabilized for the last 12 months. The mean heart rate was 79.9 beats per minute. A composite of cardiovascular death and hospitalizations was the primary endpoint. Analysis revealed that patients under ivabradine treatment had a reduction in the primary endpoint (HR: 0.82, 95% CI: 0.75-0.90; $p < 0.0001$). Patients with the highest baseline heart rate had the largest reduction in the primary endpoint [24].

A recent meta-analysis of randomized controlled trials evaluating the efficacy and safety of ivabradine in HF patients was reported. A total of 24,562 patients were included. Ivabradine reduced the heart rate (mean difference = −17.30, 95% CI: 19.52-−15.08; $p < 0.00001$), significantly increased the left ventricular ejection fraction (mean difference = 3.90, 95% CI: 0.40-7.40; $p < 0.0001$) and led to a better New York Heart Association classification. Ivabradine also improved the peak oxygen consumption, exercise capacity and 6-minute walk distance [25].

Ivabradine has also been found to increase left ventricular ejection fraction and New York Heart Functional Class in children with dilated cardiomyopathy and symptomatic HF. These positive outcomes were achieved safely. This study opens a new alternative for treating systolic HF in the pediatric population whose current pharmacological choices are limited and, in most cases, have a low level of evidence [26].

3. DRUGS UNDER INVESTIGATION

3.1 Apelin

Apelin is a vasoactive peptide associated with G protein-coupled receptor. In experimental studies, apelin has demonstrated several properties in the cardiovascular system, such

as nitric oxide-mediated vasorelaxation, positive inotropic activity and diuresis. Apelin has been tested both in experimental and human studies. Apelin concentrations are higher in failing hearts, but there is an increase after angiotensin-receptor blockers administration [27, 28]. Several apelin peptides have been identified in experimental studies, but apelin-13 is the most abundant in cardiac tissue and has been associated with APJ receptor stimulation to cause vasodilatation and positive inotropic properties. The apelin-APJ system and renin-angiotensin system have mutual interactions. Inhibition of angiotensin II type-1 receptor transcription increases APJ expression, whereas apelin transcription is reduced during angiotensin II elevation [29].

In experimental studies, apelin and APJ receptors are down-regulated and associated with left ventricular dysfunction and its administration improves cardiac contractility, left ventricular remodeling, and reduces volume overload and oxidative stress. Wang *et al.*, conducted an investigation in 7 dogs with induced HF and examined the effects of infusion of apelin-13 on left ventricular function and ventricular volumes. Dogs that received the higher doses of apelin-13 had an improvement on left ventricular ejection fraction and end-systolic volume compared to baseline (37 ± 3% *vs*. 30 ± 3% and 45 ± 4 ml *vs*. 54 ± 4 ml; $p < 0.05$ respectively). These findings were also associated with a reduced apelin concentration from 168 ± 14 pg/ml at baseline to 30,590 ± 6,586 pg/ml after high apelin dose; $p < 0.05$ [30].

Another study assessed the cardiovascular actions of prolonged apelin-13 infusion in patients with HF. Intravenous apelin-13 infusion increased cardiac index while reducing mean arterial pressure and peripheral vascular resistance index. Prolonged 6-hour apelin-13 infusion caused a sustained increase in cardiac index with increased left ventricular ejection fraction in patients with chronic HF compared with controls. These beneficial effects were maintained even in the presence of renin-angiotensin system activation which could be a promising alternative for the treatment of HF patients [31].

3.2 Anakinra

Inflammation is a well-recognized pathophysiologic factor for HF. Some inflammation mediators are commonly expressed in the failing heart as an adaptive response to volume overload and tissue damage. Some of these mediators include interleukin-1, interleukin-6 and tumor necrosis factor. Several experimental studies have demonstrated that these molecules may provoke tissue damage in cardiomyocytes and expression of HF phenotypes at high levels. These inflammatory mediators may induce cardiac remodeling by favoring myocyte hypertrophy, having negative ionotropic effects, increasing oxidative stress, upregulation of angiotensin I receptors and increasing myocardial fibrosis and necrosis [32, 33]. Despite the negative effects of inflammatory mediators on failing hearts, so far, there are no approved drugs for treating HF based on inhibition and/or blocking some of these pathways.

Interleukin-1 has been implicated as a factor contributing to systolic and diastolic HF and impairing outcomes in previous studies. Anakinra, an interleukin-1 blocker, has been tested satisfactorily in HF patients with promising results in systolic and diastolic parameters and concentrations of inflammatory markers, such as C-reactive protein [34, 35]. A recent study conducted by Van Tassell, *et al.*, evaluated the administration of anakinra on peak aerobic exercise capacity and inflammatory mediator levels in recently decompensated systolic HF patients. Sixty patients with systolic HF were randomly assigned to receive 100 mg of anakinra for 2 or 12 weeks or receive a placebo. Patients who continued anakinra treatment showed improvement in peak maximal oxygen consumption from 14.5 (10.5-16.6) to 16.1 (13.2-18.6) mL/kg/min ($p = 0.009$ for within-group changes) [36].

This same group of investigators randomized 31 patients with HF with preserved ejection fraction and high levels of C-reactive protein to receive 100 mg of anakinra daily or placebo for 12 weeks. After 12 weeks of anakinra administration, peak oxygen consumption was not different between both groups (from 13.6 [11.8-18.0] to 14.2 [11.2-18.5] mL/kg/min; $p = 0.89$) and placebo (14.9 [11.7-17.2] to 15.0 [13.8-16.9] mL/kg/min; $p = 0.40$), without significant between-group differences in changes at 12 weeks (-0.4 [95% CI, -2.2 to +1.4]; $p = 0.64$). However, C-reactive protein and NT-proBNP levels were lower in the anakinra group compared with the placebo after the competition of treatment. Although there were no positive outcomes in peak oxygen consumption after anakinra treatment, this study should encourage further investigation in this field. Reduction in baseline values of C-reactive protein and NT-proBNP levels is a noteworthy finding, but whether these changes would improve clinical and hemodynamic parameters is unknown [37].

3.3 Cenderitide

Natriuretic peptides are molecules that play a relevant role in the pathophysiology of HF. The main actions of these molecules include natriuresis, vasodilatation, hypertrophy and fibrosis regression, anti-inflammatory properties and endothelium regeneration. These properties make natriuretic peptides a promising option to treat patients with HF. Currently, there are five natriuretic peptides described: atrial natriuretic peptide, B-type natriuretic peptide, C-type natriuretic peptide, urodilatin natriuretic peptide and *Dendroaspis* natriuretic peptide. All natriuretic peptides, except C-type natriuretic peptide, bind to a particulate guanylyl cyclase A membrane-bound receptor. In the case of C-type natriuretic peptide, it binds to the particulate guanylyl cyclase B membrane-bound receptor. There is a third receptor named natriuretic peptide type-C receptor that participates in the clearance of these molecules from plasma. This action is supported by the enzyme, neprilysin, which is widely expressed in the endothelium.

The design of new natriuretic peptides represents a growing field of investigation for the treatment of HF. Cenderitide is a novel natriuretic peptide that co-targets both particulate guanylyl cyclase A and B membrane receptors. It is composed of C-type natriuretic peptide and *C-terminus of Dendroaspis* that have the property to stimulate anti-fibrotic and anti-hypertrophy processes without significant hypotension [38, 39].

At present, several experimental studies have demonstrated the beneficial effects of cenderitide, and clinical stud-

ies show that this drug lacks significant side effects. Kawakami *et al.*, carried out a randomized controlled trial in subjects with stable HF with the aim to enhance the positive effects of cenderitide and identify possible side effects. They studied 12 patients in the cenderitide group and 6 in the placebo. After 4 hours of intravenous infusion of 20 ng/kg/min of cenderitide, the findings show that this drug is safe, well-tolerated and increases significantly plasma levels of cyclic guanosine monophosphate. This study was the first to evaluate cenderitide in humans and warrants further investigations in this field [40].

3.4 Finerenone

Mineralocorticoid-receptor antagonists use represents a class I indication for treating patients with HF with reduced ejection fraction. Both spironolactone and eplerenone have been found to reduce mortality and hospitalizations in these patients [4, 5]. However, it has been observed that patients with chronic kidney disease and/or diabetes mellitus often develop hyperkalemia and worsening renal function after administration of these drugs and is a common cause of treatment discontinuation [41]. Finerenone (BAY 94-8862) is an oral, selective, non-steroidal mineralocorticoid-receptor antagonist, which combines the selectivity of eplerenone and potency of spironolactone for treating HF patients. Experimental studies in rats have demonstrated that finerenone prevents the development of structural and functional heart damage with reduced risk of hyperkalemia compared with steroidal mineralocorticoid-receptor antagonists [42].

Finerenone has been evaluated in patients with HF with reduced ejection fraction and several stages of chronic kidney disease. Finerenone reduced plasma natriuretic peptides levels and albuminuria to the same magnitude as spironolactone. Less increase in serum potassium and higher glomerular filtration rates in the finerenone group accompanied these findings. As a part of the minerAlocorticoid Receptor antagonist Tolerability Study-Heart Failure (ARTS-HF) study, Filippatos G *et al.*, evaluated oral doses of finerenone in patients with worsening HF with reduced ejection fraction, chronic kidney disease and/or diabetes mellitus. One thousand sixty-six patients were randomized to receive oral, once-daily finerenone, or eplerenone for 90 days. The primary endpoint was the percentage of individuals with a decrease of 30% in plasma NT-proBNP from baseline to day 90. A secondary endpoint was a composite of death from any cause, cardiovascular hospitalizations or emergency presentation for worsening HF. Patients treated with finerenone demonstrated a 30% or greater decrease in plasma NT-proBNP levels, and secondary endpoints were also less frequent in this group [43].

A recent meta-analysis conducted by Pei *et al.*, evaluated the efficacy and safety of finerenone compared with spironolactone and eplerenone in patients with chronic heart failure. A total of 1,520 patients were included in the analysis. The main conclusions of this study were that finerenone reduced plasma NT-proBNP levels and had anti-ventricular remodeling properties greater than another steroidal mineralocorticoid-receptor antagonist in a dose-dependent manner. Finerenone also is safer in patients with reduced glomerular filtration rates [44].

3.5 Mirabegron

Myocardial β3-adrenoreceptor is associated with a negative ionotropic effect in normal hearts and is overexpressed in failing hearts. These effects suggest that β3-adrenoreceptor agonists may have deleterious actions in patients with HF. However, β3-adrenoreceptor stimulation mediates activation of myocyte Na+-K+ pump, increasing outward Na+ and reducing intracellular Na+ concentrations. Intracellular Na+ concentrations are harmful in human hearts because of a reduction in contraction and an increase in oxidative stress. Previous studies have demonstrated that β3-adrenoreceptor agonism should have deleterious actions in normal hearts, but positive effects in failing hearts [45, 46]. Other positive effects of β3-adrenoreceptor activation include coronary vasodilatation, reduced left ventricular hypertrophy and myocardial fibrosis by coupling to the nitric oxide cyclic guanosine monophosphate pathway [47].

Mirabegron, a β3-adrenoreceptor agonist, has been approved by the Food and Drug Administration for the treatment of urgent urinary incontinence and increased urinary frequency in patients with overactive bladder with well-proven efficacy and safety profiles [48]. Bundgaard *et al.*, conducted the first-in man-randomized trial exploring mirabegron in patients with HF. This was a study of 70 patients with left ventricular ejection fraction < 40%, randomized to receive mirabegron 25-100 mg/day or placebo for six months. Patients in the mirabegron group had an increase in left ventricular ejection fraction while no increase was seen in the placebo group. Adverse side effects were uncommon [49]. Based on the positive actions of β3-adrenoreceptor activation for reducing myocardial hypertrophy, Pouleur *et al.*, are developing a randomized controlled trial (Beta3-LVH) with the aim to evaluate the benefits of mirabegron on left ventricular mass index and diastolic function in patients with hypertensive heart disease with high risk for developing HF with preserved ejection fraction [50]. If this study shows positive outcomes, mirabegron administration could represent a feasible choice for preventing HF in high-risk hypertensive patients.

3.6 Elamipretide

Failing hearts have impaired energy generation secondary to a reduced loss of adenosine triphosphate production. Low levels of adenosine triphosphate production increase reactive oxygen species and oxidative stress leading a myocardial remodeling and dysfunction. These are common pathophysiological processes seen in patients with HF. Elamipretide (MTP-131, Benda*via*) is a mitochondrial tetrapeptide that inhibits the cytochrome C/cardiolipin peroxidase complex. This process favors the transportation of electrons from complex III to complex IV and secondarily increase mitochondrial adenosine triphosphate generation and cardiac performance [51, 52]. In a canine model of HF with reduced ejection fraction, elamipretide improved left ventricular systolic function and reduced plasma biomarkers of inflammation. Long-term therapy with elamipretide (once-daily dose during 3 months) demonstrated to be effective in reverting several mitochondrial abnormalities in left ventricular tissues from dogs and humans with HF with reduced ejection fraction. In both cases, levels of cyclic

guanosine monophosphate, nitric oxide synthetase and peroxisome proliferator-activated receptor-gamma coactivator-1α (a transcription factor that drives mitochondrial biogenesis) were significantly increased after treatment with elamipretide [53]. These experimental studies demonstrated the benefits of treatment with elamipretide on several pathways that improve mitochondrial energy production and utilization and secondary cardiac function.

Recently, Daubery *et al.* [54] conducted a double-blinded placebo-controlled trial in patients with HF with reduced ejection and divided the patients into three groups for elamipretide treatment at increasing doses and placebo group. Patients were between 45 and 80 years old, New York Heart Association functional class II or III and without HF hospitalization in the preceding 3 months. All patients were being treated with guideline-based drugs for HF with reduced ejection fraction. Several clinical, laboratory, echocardiographic and safety parameters were evaluated after 6, 8, 12 and 24 hours post-infusion start. Elamipretide was safe and well-tolerated. End-diastolic and systolic volumes were significantly reduced in patients with the highest doses of elamipretide (-15,0 ± 12,4 ml, 14,1 ± 39,3 ml, 2,9 ± 11,3 ml; p = 0,009) and (-7,9 ± 6,4 ml, 9,0 ± 23,9 ml, 1,4 ± 5,9 ml; p = 0,009) respectively. Left ventricular ejection fraction, global longitudinal strain and NT-proBNP levels did not show significant differences among all groups. Further studies are necessary to demonstrate the positive hemodynamic benefits of elamipretide in patients with a daily dose treatment in long-term follow-up.

3.7 Neuregulin

Neuregulins are proteins that belong to the epidermal growth factor family. Neuregulin-1 (NRG1) is the most characterized variant, and its benefits on the cardiovascular system have been widely explored. NRG1 exerts its effects through the family of tyrosine kinase receptors (ErbB) in a paracrine manner. NRG1 binds to ErbB3 or ErbB4 receptors, which causes intracellular changes of the kinase receptors leading to activation of several intracellular pathways needed for cell maintenance and survival [55, 56]. NRG1/ErbB signaling is necessary for ventricular trabeculation, normal ventricular wall thickness, and valve formation. Experimental models in animals have demonstrated that NRG1/ErbB axis deterioration is associated with several parameters of dilated cardiomyopathy, such as ventricular dilatation, wall thinning and decreased contractility [57]. Myocyte cytoprotection has been observed in rats after treatment with NRG1 by inhibition of anthracycline-induced apoptosis [58].

NRG1 has been tested in humans for the treatment of HF with good results. Gao *et al.*, [59] assessed the efficacy and safety of recombinant human NRG1 in chronic HF patients. In this phase II randomized controlled study, 44 patients with HF with reduced ejection fraction were randomized to receive NRG1 or placebo. After 10 days of follow-up both end-diastolic volume and end-systolic volume were decreased in patients who received 0.6 ug/kg/day of NRG1 compared with baseline values (-11.58 ± 12.74%; p = 0.002 and -5.64 ± 10.03%; p = 0.05) respectively. Cardiac volumes reduction continued to decrease at day 90 of follow-up. These findings were confirmed in another study in 15 patients with stable HF with reduced ejection fraction. Cardiac output increased by 30% during acute infusion of recombinant NRG1. Also, decreases were observed in pulmonary artery wedge pressure and systemic vascular resistance [60]. These findings in humans and previous experimental studies demonstrate that NRG1 administration is associated with reverse remodeling and improvement in cardiac performance in HF with reduced ejection fraction.

3.8 Ranolazine

Ranolazine has been approved for the treatment of chronic angina by the leading cardiovascular societies. It has a class IIA recommendation for patients with stable chronic angina who remain symptomatic beyond the treatment with beta-blockers and calcium channel blockers [61, 62]. Ranolazine inhibits late inward sodium current reducing intracellular calcium overload, which is one of the primary mechanisms causing impaired relaxation of the myocytes, diastolic dysfunction and impaired coronary blood flow in diastole. This drug also inhibits fatty acid oxidation and improves the efficiency of glucose oxidation [63].

Possible benefits of ranolazine in the treatment of patients with HF have been tested in animals. Experimental studies have demonstrated that ranolazine reduces left ventricular diastolic pressure and improves left ventricular ejection fraction [64]. In mice treated with trastuzumab, co-administration of ranolazine prevented proapoptotic effects and cardiotoxicity compared with controls [65].

RALI-DF was a proof-of-concept study that evaluated the effects of ranolazine on diastolic function in patients with HF with preserved ejection fraction. Patients who received ranolazine showed a reduced left ventricular end-diastolic pressure (2.2 mmHg; p = 0.04) than placebo [66]. However, no difference in exercise tolerance and brain natriuretic peptide levels were found. Another study conducted by Murray *et al.*, [67], 109 patients with both systolic and diastolic HF demonstrated an increase in left ventricular ejection fraction and a reduction in cardiovascular events in patients receiving ranolazine. Currently, the safety of ranolazine in patients with HF is uncertain, and no recommendations exist supporting its use in these patients. Further well-designed studies with a large number of patients are needed to demonstrate the benefits of this drug in HF.

CLINICAL PERSPECTIVE AND CONCLUSION

Pharmacological therapy for treating patients with congestive HF continues to evolve. Present guidelines strongly recommend treating patients with HF with reduced ejection fraction with multiple medications proven to improve clinical outcomes as well as survival. Carvedilol, bisoprolol and metoprolol succinate are unique in that they overtime improve the ejection fraction as well as decrease mortality. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone blockade, hydralazine/isosorbide dinitrate and sacubitril/valsartan all decrease mortality. Ivabradine appears beneficial in HF patients with reduced ejection fraction and high resting heart rates after tolerated beta-blocker.

Drugs under investigation for treating patients with HF with reduced ejection fraction encompass many novel mechanisms, including vasoactive peptides, blocking inflammatory-mediators, natriuretic peptides, selective non-steroidal mineralocorticoid-receptor antagonists, myocardial β3-adrenoreceptor agonists, inhibiting the cytochrome C/cardiolipin peroxidase complex, neuregulin-1/ErbB signaling needed for myocardial cell survival and inhibiting late inward sodium current reducing intracellular calcium overload. Of note, anakinra, mirabegron, and ranolazine may also be beneficial in patients with HF with preserved ejection fraction. These novel approaches will require carefully performed double-blind multicenter trials to determine their benefit before being added to HF recommended guidelines.

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The authors declare no conflict of interest, financial or otherwise.

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