Heart Failure: A Systematic Approach under of Disease Treatment Perspective

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Abstract: The ventricular failure to fill or eject blood into the systemic circulation is characterized as heart failure (HF). HF is a severe disease that requires treatment and rehabilitation to reduce morbidity and mortality and improve the patient's life quality. However, some therapies remain incomprehensible to many professionals. The purpose of the study was to highlight the primary therapies for HF, including medications, clinical trials, physical training, dietary habits, and alternative therapies such as yoga, meditation, laughter, and Tai Chi exercise. According to PRISMA rules for systematic reviews and Clinical Trials Gov rules for clinical trials, this is a review. There are several HF treatment methods, thus applying to the specific needs of each individual, thus being able to succeed both in drug therapy as reducing heart rate, improving the N-terminal fraction of B-type natriuretic peptide and left ventricular ejection fraction, besides reducing mortality and, alternative therapy emerges as a strategy to improve depression and anxiety, especially the quality of life of patients with HF. Therefore, the treatments act to improve the quality of life of individuals. For some, even palliatively, the therapy must still be combined with a change in lifestyle by applying physical exercises and balanced nutrition. There are few clinical studies in progress in Brazil, which calls for more clinical applications with drugs in humans to discover and revolutionize the treatment of the disease.

Keywords: Heart Failure, Drug Therapy, Complementary Therapies, Clinical Trial, Cardiac Rehabilitation, Cardiovascular Diseases.

1. INTRODUCTION

The heart, a vital organ to the proper functioning of body systems, when it is unable to pump enough blood to meet the body's needs due to a deficiency in the ventricular filling or blood ejection into the systemic blood circulation, is characterized as a clinical syndrome, Heart Failure (HF) [1]. HF has a significant prevalence in primary care, reaching 10% in over 70-year-old individuals, causes a high morbimortality, reduces the patient's life quality, hospital internments and a rise in healthcare expenses [2, 3], making it a public health problem in Brazil and a high expense for the National Health System (SUS).

The primary symptoms are dyspnea when resting, fatigue, orthopnea, peripheral edema, paroxysmal nocturnal dyspnea, high jugular venous pressure (JVP), and dyspnea on exertion [4]. Some etiologies are highlighted, such as ischemic heart disease and systemic arterial hypertension (SAH); less common causes include primary or toxic cardiomyopathy, valvular or congenital lesions, right ventricular dysfunction, and arrhythmia. It is noteworthy that diabetes mellitus, hypertension, obesity, smoking and atrial fibrillation are risk factors that imply the onset of the disease [5, 6].

In most cases, the clinical picture presented by patients does not collaborate with the diagnosis because they are nonspecific symptoms for HF. Moreover, some symptoms such as high JVP and apical impulse displacement are more difficult to detect [7]. Note that HF can be characterized according to the ejection fraction, whether low, intermediate or high (Figure **1**), and can be classified concerning the severity of symptoms and the disease evolution time that takes different stages [8].

Thus, some tests facilitate the HF diagnosis, the echocardiogram and the electrocardiogram. These

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tests can show the heart rhythm, electrical conduction, left ventricular hypertrophy, even the characteristic Q waves, having predictive value for the diagnosis and laboratory tests aimed at the treatment, such as blocking the renin-angiotensin-aldosterone system. Also, natriuretic peptides must be observed to assess the concentration, check if the heart is sick or if some heart chamber's load is increased, and the chest radiography that shows pulmonary venous congestion or edema of the individual with HF [9, 10].

As for treatment, potassium reducing agents may allow initiation and titration of mineralocorticoid antagonists in a more significant proportion of patients. Meta-analysis studies suggest better results with ferric carboxymaltose in patients with iron deficiency. Medications effective in heart failure with reduced ejection fraction (HFEFr) may also be helpful in HF with mid-interval ejection fraction [11]. It should be reported that the study will not address only this treatment section, but the most relevant HF treatment aspects are produced in this paper.

Being the most common pathology in the elderly, it ranks among the diseases of high incidence and mortality and, in addition, therapies capable of causing significant changes in the patient's life quality remain unknown to many professionals, which emphasizes the role of the multidisciplinary team in improving the patient's health in such condition. Thus, the study approaches a careful analysis of these two topics, "HF and treatment", aiming to evidence the HF treatment, including medications, physical training, eating habits and alternative therapies, this way, new data are transcribed, and a summary of recent findings are provided in the paper.

2. METHODOLOGY

2.1. Study Design

The systematic review was chosen for the scientific investigation of conventional and alternative therapies for HF. MeSH adopted the search strategy by six descriptors described in subsection 2.2. This research

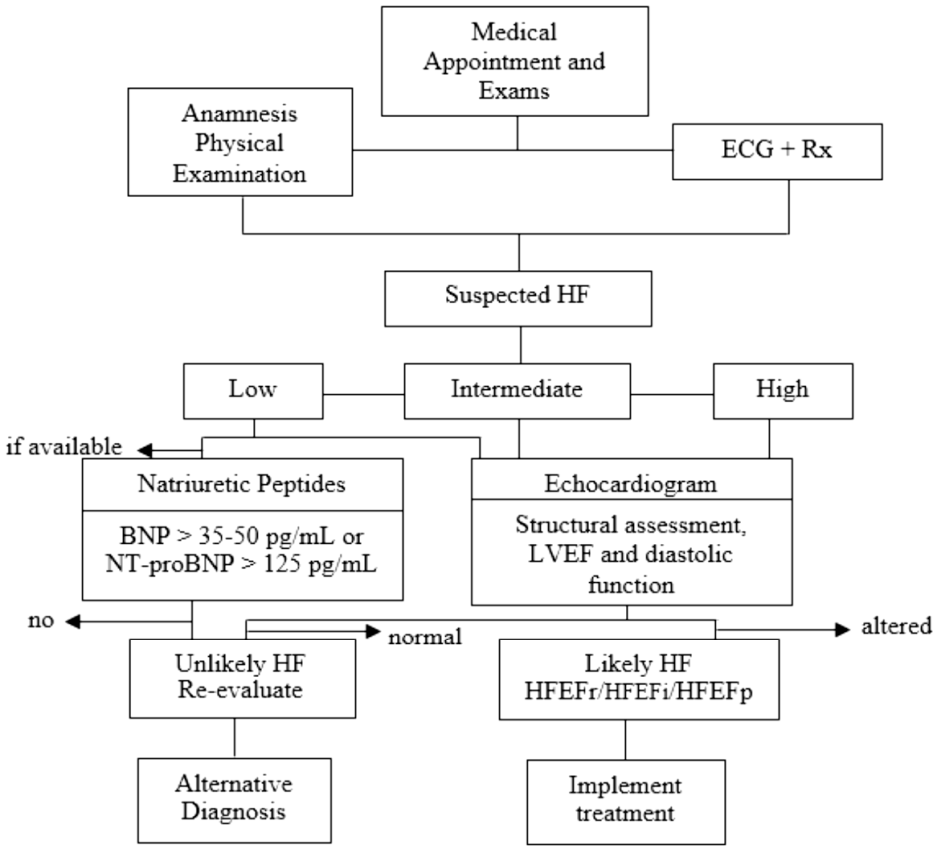

Figure 1: Flowchart for the Heart Failure diagnosis.

Legend: (ECG) Electrocardiogram; (Rx) X-ray; (HF) Heart failure; (BNP) B-type natriuretic peptide; (NT-proBNP) N-terminal fraction of B-type natriuretic peptide; (LVEF) Left ventricular ejection fraction; (HFEFr) Heart failure with reduced ejection fraction; (HFEFi) Heart failure with intermediate ejection fraction; (HFEFp) Heart failure with preserved ejection fraction. Adapted source: Rohde *et al*. [12].

was conducted in the period from October 2020 to September 2021. Three hundred one studies were checked and subjected to eligibility analysis, and at the end, 67 studies were selected according to PRISMA rules (Figure **2**) (HTTP: //www.prisma-statement.org/).

2.2. Databases and Research Strategy

The electronic databases Virtual Health Library, PubMed, and Cochrane Library, were searched using the keywords: Heart Failure, Drug Therapy, Complementary Therapies, Clinical Trial, Cardiac Rehabilitation, Cardiovascular Diseases. Additionally, a combination of the keywords with "AND" and the Boolean operator "OR" was used. After searching for the terms in MeSH, clinical trial information was obtained from Clinical Trials Gov (https://clinicaltrials.gov/).

2.3. Study Selection and Bias Risk Assessment

Full-text articles from 2005 to 2021 in English were selected, including titles and/or abstracts related to HF treatment/therapies. Monographs, dissertations, theses and unavailable articles were excluded from the study and articles repeated in electronic databases. After the selection, the bibliographic references of the selected articles were analyzed and classified for the study according to the proposed theme. Twelve independent reviewers carried out the research. Research and article selection: reviewers VLR, APAC, RRCS, and LLAA. The final decision on the selection of articles: reviewer RRR. Organization of the study and data collection: reviewers LAF, MMS, JPFET, HGPS and RRR. Article writing: Reviewers IPPG, LFGS, MMS, LLAA, RRR. Manuscript supervision: reviewers VLR, APAC, LAF, RRCS, and HGPS. Critical revision and approval of the final version of the manuscript: reviewer RRR and JMPG.

3. LITERATURE REVIEW AND DISCUSSION

The literature findings compendium synthesizes the qualitative data of the systematic review on the aspects that the therapeutic process can help in HF, improving the patient's life quality. Thus, according to the systematic search, 301 references were identified through electronic searches in different databases. After removing duplicate references, there were 185

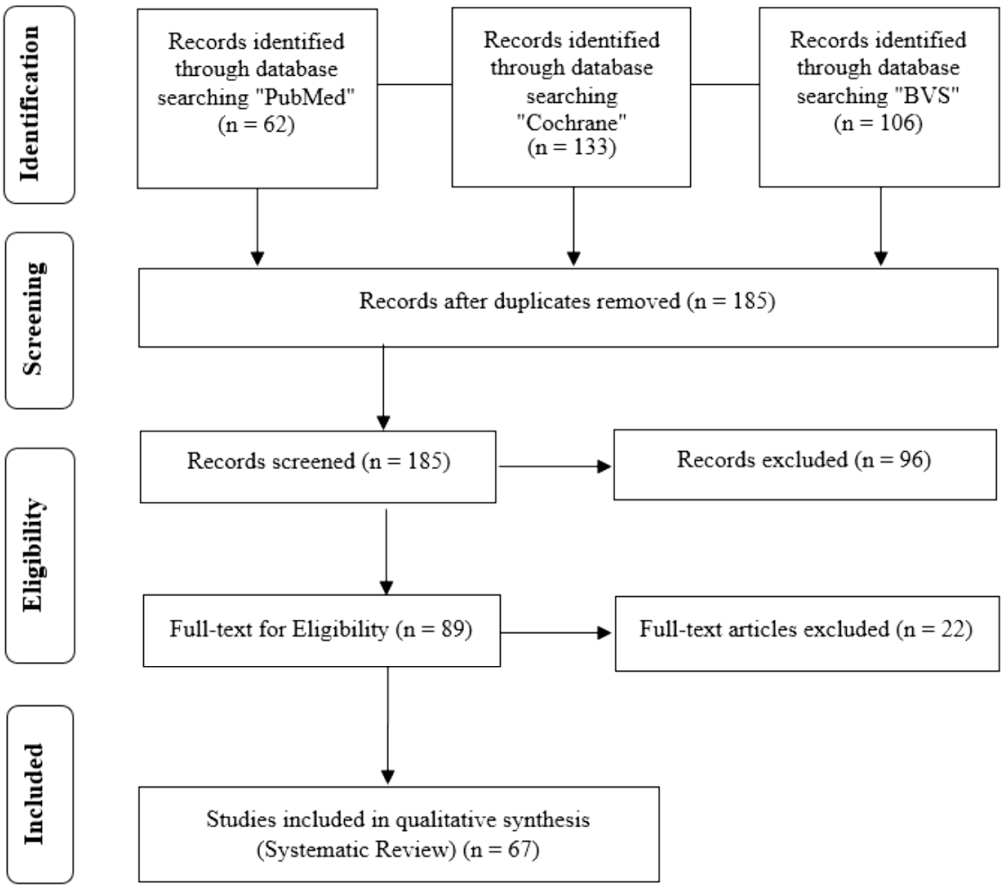

Figure 2: Flowchart.

references. Ninety-six irrelevant references were excluded by reading the abstracts. A total of 89 references were retrieved for further evaluation of the complete publication. A total of 22 references listed in the category 'Full-text articles, with justification' were excluded, leaving 67 references that met the inclusion criteria (Studies included in the qualitative overview). The reference flow chart is shown in Figure **2**.

3.1. Main Drug Treatment Approaches

3.1.1. Vericiguat

Vericiguat augments the cyclic guanosine monophosphate (GMP) route by stimulating oral soluble guanylate cyclase (sGC), a key enzyme in the nitric oxide (NO) signaling route. Thus, the GMP route directly stimulates sGC via a NO-independent binding site, sensitizing sGC to endogenous NO when it stabilizes NO binding at the binding site. Furthermore, these agents modulate sGC independently of NO, mimicking it and restoring cyclic GMP signaling, which will cause vasodilation of cardiac vessels. This increase in the sGC in the nitric oxide route serves as a therapeutic target for chronic HF. It is worth noting the importance of cyclic GMP, which acts as a regulator of myocardial energy, cardiac performance, and endothelial function [13, 14].

Therefore, in a clinical trial involving individuals with high-risk HF, patients were given a dose of 2.5 mg/d and then titrated to 10 mg/d. It was found to have improved hospitalization rates. However, vericiguat had no statistically significant effect on changing the NT-proBNP level at 12 weeks [15, 16].

3.1.2. Sacubitril-Valsartan

Presently, pharmacological therapies have been tested concerning the renin-angiotensin-aldosterone system to reduce HF mortality. In 2014, in a prospective study on ARNI (angiotensin II receptor blocker neprilysin inhibitor) with ACE inhibitors (angiotensin-converting enzyme inhibitor) versus enalapril (PARADIGM-HF) in order to ascertain the impact on morbidity and mortality and, it was found that the molecule LCZ696 acts as an angiotensin receptor blocker via valsartan and neprilysin inhibition via sacubitril significantly reducing mortality and hospitalizations [17-20].

These treatments have shown promise; however, the earlier the disease is diagnosed, the sooner the best treatment can be started.

3.1.3. Carvedilol

The β-adrenergic antagonists are a class of drugs widely used in HF treatment. One of the most widely used and significantly responsive is the nonselective beta-blocker Carvedilol. This drug has vasodilator properties, and its use improves the left ventricular (LV) ejection fraction [21]. This improvement is observed during 6 to 12 months of treatment, especially in the chronic HF case. It was also observed during clinical trials an attenuation of the remodeling that the LV suffered in HF and positive results in the treatment of patients who developed the disease after acute myocardial infarction (AMI) or in those who have already suffered LV dysfunction. Studies show that it may have pleiotropic effects as an antioxidant, antiarrhythmic, and increase insulin sensitivity. The clinical benefits and high safety of this drug reduce the number of hospitalizations, besides providing the patient with a better life expectancy. Therefore, the use of Carvedilol in the treatment of HF is an acceptable therapeutic form [22].

Although Carvedilol is considered one of the best β-adrenergic antagonists in HF treatment, its cost is expensive. This impacts the disease's treatment, as patients who cannot afford it often abandon the medication. The medication discontinuation increases the cases of decompensated HF and, in the long term, there is a loss of benefits in cardiac recovery. A socioeconomic alternative is Propranolol, available for free through the National Health System (SUS). Clinical studies show the efficacy of this drug in improving hemodynamic parameters and ventricular remodeling and increasing the ejection fraction. Moreover, in patients who are already in stable drug treatment with Carvedilol, including high-dose and chronic use, the drug substitution by Propranolol has a low intolerance rate, and no change in life quality and functional capacity has been observed. This substitution is also not associated with any impairment of LV systolic function. Thus, when the patient does not have the socioeconomic resources to treat HF with Carvedilol, Propranolol is a therapeutic option indicated and made available by SUS [23].

It is found in randomized clinical trials by Flannery *et al*. [24], a strong correlation between heart rate (HR) reduction, LVEF improvement, and mortality reduction, which confirms the Marques *et al*. data [23].

3.1.4. Vitamin D

In epidemiological data, it has been observed that, in HF patients, the vitamin D serum level is lower in

contrast to a non-HF patient [25-27]. This is because vitamin D deficiency affects the cardiovascular system, contributing to left ventricular remodeling, myocardial fibrosis, inflammation, and HF aggravation. It is also related to the renin-angiotensin-aldosterone system, which can cause an inflammatory response and endothelial dysfunction [28-31].

In 2014, Dalbeni *et al*. [32] conducted a double-blind, randomized, controlled study in which three doses of cholecalciferol, vitamin D3, were used over 25 weeks. The significant Vitamin D level in plasma doubled at the end of these six months to 31.7 ng/mL. The experimental data showed a reduction in ventricular hypertrophy and that it probably promotes a decrease in hypertension, plus it improved the cardiac ejection fraction of HF patients.

In 2019, Wang *et al*. [33] sought not only a solution for HF through vitamin D but also how it could decrease mortality, increase left ventricular ejection fraction, alter levels of C-reactive protein, which has normal levels between 0.3 mg/dL and 3.0 mg/dL, if more prominent than that, it indicates an inflammatory or infectious process, and can also function as an assessment of whether or not a person is at risk of developing cardiovascular disease, and an improvement in life quality. A meta-analysis observed ten studies conducted between 2006 and 2017 that used vitamin D as a possible HF treatment. The results showed that vitamin D supplementation improves life quality and decreases the C-reactive protein level, which decreases inflammation levels, but showed no improvement in the mortality issue and left ventricular ejection fraction compared to conventional treatments. However, when vitamin D was administered without calcium supplementation, left ventricular ejection fraction improvement was observed because excess calcium in plasma can cause cardiac dysfunction [34].

Hence, from these studies, it is feasible to include vitamin D as a possible treatment to improve a person's life quality with HF. However, there is still a lack of further studies that can prove its use compared to other conventional treatments.

3.1.5. Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme inhibitors (ACEI) are a drug group with proven benefits in the evolution of HF patients, both in terms of morbidity and mortality and improvement in life quality. Considering that angiotensin predisposes to the development of left ventricular hypertrophy by reducing relaxation and increasing ventricular rigidity, it can be said that drugs that modulate this system may consequently diminish the smooth muscle cell growth, reduce the collagen deposition and the growth factor expression and, finally, decrease the LV mass, besides being accompanied by an improvement in the diastolic dysfunction [12].

The use of ACE inhibitors is supported for different HF etiologies and patients with left ventricular dysfunction after myocardial infarction, patients with asymptomatic left ventricular dysfunction. Another alternative medication is angiotensin II receptor blockers, which have comparable efficacy and are indicated for intolerant or allergic to ACE inhibitors. The simultaneous use of these drugs causes significant

Table 1: Target Doses of Heart Failure Medications

	Medication	Starting dose (mg)	Target dose (mg)
ACEI	Captopril	6.25 mg TID	50 mg TID
	Enalapril	2.5 mg BID	10-20 mg BID
	Fosinopril	5-10 mg QD	40 mg QD
	Ramipril	1.25-2.5 mg QD	10 mg QD
	Lisinopril	2.5-5.0 mg QD	20-40 mg QD
	Trandolapril	1 mg QD	4 mg QD
	Quinapril	5 mg BID	20 mg BID
ARB II	Candesartana	4-8 mg QD	32 mg QD
	Losartan	25-50 mg QD	50-150 mg QD
	Valsartan	20-40 mg BID	160 mg BID

(ACEI) Angiotensin Converting Enzyme Inhibitors; (ARB II) Angiotensin Receptor Blockers II; (TID) 3 times daily; (BID) twice daily; (QD), once daily. **Fonte adaptada:** Yancy *et al.* [36].

adverse effects, so the combination of medications should be avoided [35].

Some aspects should be considered in the medication use, such as intolerance to ACE inhibitors, persistent and debilitating cough, or angioedema. In these cases, ACE inhibitors should be introduced at low doses until the target dose (Table **1**) is reached, which guarantees the benefits. In these cases, careful monitoring of renal function and potassium levels is recommended. If there are excesses, the medication should be discontinued [35].

3.2. Clinical Trials

One thousand one hundred eighty-nine clinical trials were found in Clinical Trials.gov. Table **2** shows the number of included studies in each region of the world [37]. The guiding issue observed in Clinical Trials.gov is that it does not have a relevant clinical trials number, especially in South America, where there are 35 clinical trials in Brazil with several studies in the recruitment process; unknown; not available; completed without results; active, not recruiting; terminated; and few completed studies with results, and still many results of phases 1, 2 and 3 have not been published, which makes it difficult to search for evidence obtained from clinical trials in reliable databases.

Regarding these numerous studies, different studies are observed with various medication sources and therapeutic methods that can be used to improve the patient's functional systems and life quality safely; thus, drug therapy is one of the most influential and favorable solutions for HF.

In 2016 [38], the drugs sacubitril and valsartan were used in a clinical trial with 1009 patients with HFEFr diagnosis, aiming to describe the patient population with HFEFr receiving treatment with sacubitril/valsartan (Clinicaltrials.gov, NCT02957409). It is believed that the administration method of these drugs may be safe, but it should test the safety, possible side effects, and drug efficacy. It is worth noting the primary outcome measures, which is to describe baseline levels of NT-proBNP, or BNP, to total all-cause hospitalization or mortality in patients with HFEFr treated with sacubitril/valsartan. However, the clinical effect needs to be verified subsequently. Thus, the research advocates secondary outcome measures, looking at symptomatic hypotension reported by the treating physician and defined, but not limited, as severe dizziness or fainting, lack of concentration, blurred vision, nausea, cold, clammy, pale skin, and rapid shallow breathing. Hyperkalemia is defined by serum potassium concentration > 5.5 mmol/L [mEq/L] after a repeat measurement to confirm serum potassium rise within a week. Renal impairment, defined as a decrease in estimated glomerular filtration rate (eGFR) of ≥ 40% after evaluation (verified at the subsequent visit) of potentially reversible causes of renal dysfunction or end-stage renal disease or need for dialysis or renal transplantation.

Several clinical trials with drug therapy are in progress in HF patients (Table **3**); however, many results have not yet been published, but it is noted that in preclinical trials in humans with HF, good results have been obtained.

3.3. Exercise and Diet

The loss of exercising tolerance is the primary chronic symptom in HF patients, directly correlated to the decrease in VO_2 max and, consequently, to the reduction in life quality and increased death risk. Therefore, exercise-based cardiac rehabilitation (EBCR) is a recommended form of treatment for stable patients, reducing HF patients' hospitalization. It has proven to be an effective method to improve peak VO_2 and muscle strength. However, a tiny fraction of eligible patients to participate in a rehabilitation program is recommended for treatment with EBCR after hospital admission [39].

The use of EBCR is an effective way to improve the prognosis of patients with cardiovascular disease. To this end, the prescribing of protocols based on high-intensity interval training has proven effective in

Table 2: Clinical Studies of HF and Localization

Region	Africa	Central America	East Asia	Japan	Europe	Middle East	North America	Canada
n[1]	18	13	121	33	505	57	473	96
Region	**Mexico**	**EUA**	**North Asia**	**Pacifica**	**South America**	**South Asia**	**Southeast Asia**	
n[1]	13	427	42	45	50	22	26	

[1]Number of studies located in each region. **Fonte adaptada:** https://ClinicalTrials.gov.

Table 3: Ongoing Clinical Trials of Medication in Patients Suffering from Heart Failure, at Clinicaltrials.gov.

nº, start and last (date) study update	Title	n[1]	Age	Intervention / Dosage	Placebo	Outcome Measures	
						Primary	Primary
NCT02957409 May 2016 March 2021	Patient registry assessing effectiveness and safety of heart failure treatment with LCZ696 across Canada	1009	≥ 18 years	starting dose: 49 mg sacubitril / 51 mg valsartan (2x); target dose: 97 mg sacubitril / 103 mg valsartan (2x)	No	NT-proBNP or BNP levels	Symptomatic hypotension; hyperkalemia; renal impairment; NT-proBNP or BNP level; mortality; hospitalization
NCT00219011 May 2005 May 2017	A twelve-week, randomized, double-blind, multi-center, placebo controlled, parallel group study to evaluate the safety and efficacy of aliskiren 150 mg when added to standard therapy in hypertensive patients with stable heart failure	280	≥ 18 years	150 mg aliscireno (1x)	Yes	Measurement of safety information and tolerability of drug after 12 weeks	Biochemical markers NT-proBNP and BNP; change in aldosterone; forces of the circulation of blood as measured by echocardiography; mean systolic and diastolic blood pressure
NCT04252937 December 2019 March 2021	A dose escalation evaluation of safety and tolerability of adrecizumab - a humanized monoclonal antibody against adrenomedullin (ADM) in patients with acute heart failure requiring hospitalization	30	≥ 18 years	0,5 mg/kg, 2 mg/kg e 8 mg/kg HAM8101 (Adrecizumabe) (1x)	No	Treatment-emergent SAEs	In-hospital assessment of AHF
NCT02275013 January 2006 October 2014	Levosimendan administration and outcome in cardiac surgery	159	≥ 18 years	Levosimendan / dose (not provided)	No	In-hospital mortality and 1 year follow-up mortality	Duration of mechanical ventilation; incidence of renal dysfunction; incidence of renal replacement therapy

[1]Number of total participants; (nº) ClinicalTrials.gov Identifier; (SAEs) Serious Adverse Events; (AHF) Acute Heart Failure; (BNP) B-type natriuretic peptide; (NT-proBNP) N-terminal pro-B-type natriuretic peptide.

improving cardiac function and peak VO_2 and can also be prescribed in conjunction with moderate-intensity continuous training [40].

The dietary caloric value should be represented by about 50 to 60% of carbohydrates, preferably with a low glycemic load, once insulin resistance can be aggravated by the carbohydrate excess, especially those with high blood glucose index. Insulin resistance, in turn, can aggravate sodium and water retention due to the natriuretic properties of the hormone [41].

The same authors report that the calorie/gram nitrogen balance should be between 120 and 160. The protein needs for HF patients are indicated at 1.1g/kg/day for healthy patients and 1.5 to 2g/kg/day for patients with nutritional deficiencies or with losses due to intestinal malabsorption or nephropathy, with edema-free bodyweight admission. Lipids should not exceed 30% of the diet's caloric value, with monounsaturated and polyunsaturated lipids preference. Sodium intake should be a maximum of 2-3g/day for patients with severe HF.

3.4. Alternative Therapies

3.4.1. Yoga

HF patients who practice physical activities improve oxygen (O_2) consumption, life quality and decrease hospitalizations. So, different types of exercises such as yoga, hydrotherapy, and dance are used. Therefore, the yoga practice can be considered a relaxation and meditation technique based on exercises, postures, adequate breathing. Thus, such performances bring many benefits in treating some diseases such as depression, breast cancer, chronic low back pain, and hypertension [42].

For Guddeti *et al*. [43], yoga therapy is a practice known to reduce HR and blood pressure (BP) in HF patients, mainly through improving physical functioning

such as balance, strength and endurance. Hence, this therapy is suggested to assist in the HF treatment.

3.4.2. Laughter Therapy

Laughter cannot cure disease, but it can help patients and physicians cope with the illness stress and moderate the patient's response to pain [44]. However, promising data from laughter therapy was found in the studies by Yoshikawa *et al.* [45]. Laughter therapy intervention resulted in a significant decrease in systolic blood pressure (SBP) and heart rate, accompanied by a significant increase in plasma serotonin concentration, depression relief and improved sociability and activeness in older people. The results of these findings suggest that laughter therapy has an effect not only on psychological function but also on physiological function, and maybe a suitable treatment to improve life quality in older people with deteriorating daily living activities and deteriorated mental health due to depressive feelings, impaired cognitive function, reduced vitality, and poor social activity.

Yet another relevant aspect is that laughter has an inversely proportional correlation with coronary artery disease, it is cardioprotective. Humorous individuals were able to decrease the catecholamine index, the frequency of arrhythmias, and the incidence of AMI [46,47].

Given these facts, it is pointed out that laughter is an alternative therapy, not a medication, therefore, it is a very low cost therapy, does not require specialized infrastructure, which suggests exposure to comedy movies and music. Also, it improves metabolic energy expenditure and immune system function, and is very promising for the care of individuals who require cardiac rehabilitation.

3.4.3. Transcendental Meditation

Meditation is an ancient practice directly associated with several religions such as Christianity, Hinduism, Islam, Buddhism, and Judaism. There are multiple ways to meditate, it varies according to the culture and the individual's religion, which makes it difficult for scientific studies to associate this practice with cardiac comorbidities [47].

Regular practice of Transcendental Meditation (TM) may have the potential to reduce SBP and diastolic blood pressure (DBP) [48], which indicates clinically significant changes in the patient's life quality [49].

In the systematic study by Précoma *et al.* [50], patients had SBP reduced by 4 mmHg and DBP by 2 mmHg. The authors describe that it is not known what actually led to the BP reduction, but their study reports that this practice leads to neurophysiological changes that over time may act on the autonomic nervous system responsible for BP control.

Based on these findings, meditation can be considered one of the practices capable of altering stress, respiratory rate, O_2 consumption, carbon dioxide elimination, and SBP, leading to a possible improvement in the sympathovagal balance [51-53]. In addition to demonstrating benefits for the BP reduction, the meditation practice brings techniques to calm the mind, quietness, self-control and behavior, which can improve certain aspects of the individual's life quality [54].

Few scientific papers have been found considering TM as an alternative therapy to improve life quality and reduce emotional stress, but suggests more clinical studies to confirm the hemodynamic data of HF patients.

3.4.4. Tai Chi Exercise

As an adjunct to treatment, Tai Chi has been found to have potential patient clinical benefits, including improved exercise self-efficacy. Large clinically significant changes in life quality are still observed, moreover, given the relationship between depression and HF, mood improvement is also highly relevant [55].

In another study it is observed improvements in life quality, mood, decreased anxiety and patients with their own ability to complete the exercises [56, 57], which confirms the Yeh *et al*. similar data [55].

Importantly, there are few scientific studies that show the clinical and patient functional status with Tai Chi exercise, which suggests more studies that prove the effectiveness of this exercise as an alternative therapy.

3.5. Sodium-Glucose Co-Transporter 2 Inhibitors

Recent studies support the benefit of the molecule "SGLT2i" (sodium-glucose cotransporter 2 inhibitors) as a therapy strategy in HFEFr patients [58].

In the studies of Zannad *et al.* [59] the authors evaluated two molecules, dapagliflozin known as DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) and empagliflozin

(EMPEROR-Reduced). The authors suggest that these agents improve the results of the patient and reduce the causes of cardiovascular death in patients with HFEFr [59]. To confirm these data, the studies by Verma *et al.* [60] stand out with the use of EMPEROR-Reduced and McMurray *et al.* [61] with DAPA-HF. The authors report that empagliflozin reduced the outcomes of severe heart failure in various doses and combinations of disease-modifying therapies for HFEFr, and also suggest that the drug can be considered as a conventional therapy in patients with HFEFr, regardless of existing baseline therapy [60]. McMurray *et al.* [61] they used DAPA-HF in a trial with patients with heart failure and reduced ejection fraction. The trial reveals how patients who received DAPA-HF had a lower risk of worsening of heart failure or death from cardiovascular causes and better symptom scores than those who received placebo [61].

These effects can be explained by the mechanism of action of SGLT2i that act in the improvement of left ventricular tension secondary to the reduction of preload with the effect of natriuresis and oshometic diuresis and postload, with improvement of endothelial function and reduction of blood pressure. We also highlight the improvement of the metabolism and bioenergetics of cardiomyocytes, showing greater ketogenesis and increased supply of β-hydroxybutyrate, inhibition of myocardial sodium-hydrogen pump, leading to higher concentration of calcium in the mitochondria, reduction of cardiac necrosis and fibrosis with inhibition of collagen synthesis, in addition to changes in the production of cytokines and epicardial adipose tissue [62-69].

Because it is a recent molecule for therapeutic use of HFEFr and has good results, other clinical trials are suggested to confirm the actions of DAPA-HF and EMPEROR-Reduced in patients with severe heart failure.

4. CONCLUSION

People with HF need treatment and rehabilitation to reduce morbidity and mortality and improve life quality. It is a serious disease with a high incidence in the population, especially in the elderly. Depending on the treatment, the therapy becomes unfeasible due to the patient's financial conditions. For low-income patients, it is necessary to be assisted by the SUS program, this way, it will maintain the therapeutic bond and humanized assistance to the patient.

There are numerous methods of treating heart failure, applying to the specific needs of each individual, and both drug therapy and alternative therapy can be successful. Some of the treatments listed work to improve the individual's life quality, and for some, even palliatively, the therapy must still be combined with a change in lifestyle by applying physical exercise and balanced nutrition. Thus, the professional contribution of doctors, nurses, physical therapists, and nutritionists is fundamental for the monitoring and observation of the patient's clinical and functional functions in heart failure therapies, hence the importance of reviewing the physical examination and a good anamnesis of the patient every 5 weeks.

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POTENTIAL CONFLICT OF INTEREST STATEMENT

The authors declare to have no conflict of interest.

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