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Chronic heart failure: a review of pharmacotherapy management

Insuficiência cardíaca crônica: uma revisão do manejo farmacoterapêutico

Insuficiencia cardíaca crónica: una revisión del manejo farmacoterapéutico

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Abstract

To evaluate, describe and compare the pharmacological treatments available for heart failure (HF). This is a literature review about the pharmacological treatment of HF based on articles selected from the PubMed database, as well as relevant guidelines, using pertinent keywords and application of inclusion and exclusion criteria. Chronic heart failure is a common condition that, if untreated, harms quality of life and is associated with a high risk of mortality, morbidity, and recurrent hospitalization. However, the prognosis of patients with this condition has been improved with knowledge of the pathophysiology of HF and, therefore, assertive application of both non-pharmacological and pharmacological treatment recommendations. Pharmacotherapy is based on neurohormoral inhibition of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system to improve the health status and survival of these patients. Currently, the recommendation for the treatment of HF with reduced ejection fraction (HFrEF) includes 4 drug classes: an angiotensin/neprilysin receptor inhibitor (ANRi), beta-blockers, mineralocorticoid receptor antagonists (MRA) and SGLT2 inhibitors (SGLT2ii). Mortality-reducing pharmacotherapy in HF currently includes ANRi, beta-blockers, MRA and SGLT2. Therefore, the challenge is to transform the results achieved in clinical studies into reality for the majority of patients with HF. This path must be promoted through multidisciplinary care

with improved access to recommended drugs, close monitoring of patients, healthy habits, control of comorbidities and therapeutic adherence.
Keywords: Congestive hearth failure; Heart failure with reduced ejection fraction; Pharmacotherapy; Neprilysin; Angiotensin receptor antagonists; Inhibitor sodium-glucose transporter 2.

Resumo

Avaliar, descrever e comparar os tratamentos farmacológicos disponíveis para insuficiência cardíaca (IC). Trata-se de revisão da literatura sobre o tratamento farmacológico da IC baseada em artigos selecionados na base de dados PubMed, bem como em diretrizes relevantes, usando palavras-chave pertinentes e aplicação de critérios de inclusão e exclusão. A insuficiência cardíaca crônica é uma condição comum que, se não tratada, prejudica acentuadamente a qualidade de vida e está associada a alto risco de mortalidade, morbidade e hospitalização recorrente. No entanto, o prognóstico dos pacientes com esta condição vem melhorando com o conhecimento da fisiopatologia da IC e então, aplicação assertiva de vias de tratamento tanto não farmacológico quanto farmacológico. A farmacoterapia baseia-se na inibição neuro-hormoral do sistema renina-angiotensina-aldosterona (SRAA) e do sistema nervoso simpático para melhorar o estado de saúde e a sobrevida desses pacientes. Atualmente a recomendação para o tratamento da IC com fração de ejeção reduzida (ICFEr) inclui 4 classes de medicamentos: um inibidor da neprilisina e antagonista do receptor de angiotensina II (INRA), betabloqueadores, antagonistas de receptores de mineralocorticóides (ARM) e inibidores de SGLT2 (iSGLT2). A farmacoterapia redutora de mortalidade na IC, atualmente, inclui INRA, beta-bloqueador, ARM e iSGLT2. Portanto, o desafio é transformar os resultados alcançados nos estudos clínicos em realidade para a maioria dos pacientes com IC. Este caminho deve ser promovido através do atendimento multidisciplinar com melhora do acesso aos medicamentos preconizados, acompanhamento próximo dos pacientes, hábitos saudáveis, controle de comorbidades e adesão terapêutica.
Palavras-chave: Insuficiência cardíaca congestiva; Insuficiência cardíaca com fração de ejeção reduzida; Farmacoterapia; Neprilisina; Antagonista do receptor de angiotensina II; Inibidor do transportador 2 de glucose-sódio.

Resumen

Evaluar, describir y comparar los tratamientos farmacológicos disponibles para la insuficiencia cardíaca (IC). Metodología: Esta es una revisión de la literatura sobre el tratamiento farmacológico de la IC basada en artículos seleccionados de la base de datos PubMed, así como guías relevantes, utilizando palabras clave relevantes y la aplicación de criterios de inclusión y exclusión. La insuficiencia cardíaca crónica es una condición común que, si no se trata, deteriora notablemente la calidad de vida y se asocia con un alto riesgo de mortalidad, morbilidad y hospitalización recurrente. Sin embargo, el pronóstico de los pacientes con esta patología ha ido mejorando con el conocimiento de la fisiopatología de la IC y, por tanto, con la aplicación asertiva de vías de tratamiento tanto no farmacológicas como farmacológicas. La farmacoterapia se basa en la inhibición neurohormoral del sistema renina-angiotensina-aldosterona (SRAA) y del sistema nervioso simpático para mejorar el estado de salud y la supervivencia de estos pacientes. Actualmente, la recomendación para el tratamiento de la IC con fracción de eyección reducida (ICFEr) incluye 4 clases de fármacos: un inhibidor de neprilisina y antagonista del receptor de angiotensina II (INRA), betabloqueantes, antagonistas de los receptores de mineralocorticoides (ARM) e inhibidores de SGLT2 (iSGLT2). La farmacoterapia reductora de la mortalidad en la IC actualmente incluye INRA, betabloqueantes, ARM e iSGLT2. Por tanto, el desafío es hacer realidad los resultados obtenidos en los estudios clínicos para la mayoría de los pacientes con IC. Este camino debe promoverse a través de una atención multidisciplinar con un mejor acceso a los medicamentos recomendados, seguimiento estrecho de los pacientes, hábitos saludables, control de comorbilidades y adherencia terapéutica.
Palabras clave: Insuficiencia cardíaca; Insuficiencia cardíaca con fracción de eyección reducida; Farmacoterapia; Neprilisina; Antagonista do receptor de angiotensina II; Inhibidor do Transportador 2 de sodio-glucosa.

1. Introduction

Chronic Heart Failure (CHF) is a serious heart disease, and is related to structural and/or functional cardiac abnormalities, hereditary or acquired, that lead to decreased efficiency of filling and ventricular ejection of blood to the body. The term “chronic heart failure” reflects the progressive character of the disease, whose initial phase is due to the compensatory activation of neurohormonal pathways and the renin-angiotensin-aldosterone system (RAAS) to maintain blood pressure and cardiac output. However, with this continuous and long-term activation, they cause hypertrophy and myocardial remodeling, leading to reduced ventricular performance, increased sodium and water retention and advancement of heart failure (HF) (Braunwald, 2013; Campelo et al., 2018; Heidenreich et al., 2022).

The main characteristics of this heart disease are orthopnea, dyspnea associated with exertion, peripheral edema and

pulmonary congestion. These symptoms provide important clinical data to establish the diagnosis through clinical history and physical examination. In addition, the diagnosis can also be performed using invasive diagnostic methods: biomarker dosage cardiac natriuretic peptides BNP and NT-proBNP, transesophageal echocardiography and cardiac scintigraphy; and non-invasive by visualizing the heart chambers and blood flow by echocardiography, electrocardiogram at rest, cardiopulmonary stress test and chest radiography that allow the quantification and detection of the degree of myocardial dysfunction and confirmation of the diagnosis of heart failure (Kamel et al., 2001; Rohde et al., 2018). Beside this, there are some factors that contribute to the increase in the occurrence of CHF and are called cardiovascular risk factors: arterial hypertension; increased serum concentrations of very low density lipoproteins (VLDL) and low density lipoproteins (LDL-c); smoking; chemotherapy or other cardiotoxic medications; diabetes mellitus; sedentary lifestyle; obesity; heredity and stress (Araújo et al., 2013; Heidenreich et al., 2022).

To stratify and plan the therapeutic management of the patient, HF has classifications according to 1) the stages of progression and development of the disease prepared by the American College of Cardiology/American Heart Association (ACC/AHA), 2) the characterization of symptoms and functionality of the patient by the New York Heart Association (NYHA) classification and 3) by left ventricular ejection fraction (LVEF) being HF with preserved ejection fraction (HFpEF) that with LVEF ≥50%, HF with mildly reduced EF (HFmrEF) with LVEF than 41% to 49%, HF with improved EF (HFimpEF) previous LVEF ≤40% and a follow-up measurement of LVEF >40% and HF with reduced EF (HFrEF) that LVEF ≤40% (Rohde et al., 2018; Kuster & Pfister, 2019; Heidenreich et al., 2022)..

HF still affects more than 23 million people worldwide and 6.4 million people in Brazil, so it is a fact that CHF is an important factor of morbidity and mortality prevalent in public health, either because of the number of affected individuals or the incidence of the disease. in the population. Regarding the economy, the management of HF is expensive due to recurrent hospitalizations and consultations and the loss of productive capacity of affected individuals (Feitosa & Carvalho, 2000; Siqueira et al., 2017; Campelo et al., 2018; Rohde et al., 2018)

Records from the Department of Informatics of the Sistema Único de Saúde (DATASUS) showed that cases of HF persistently increases in Brazil, and in 2021 there were 163,315 hospitalizations for heart failure and 22,011 deaths, with expenses in the hospitalization service of R$ 330,847 938.03 to the country. In addition, the population over 60 years old represents approximately 72% of hospitalizations for HF and 82% of deaths in 2021, in addition to that, epidemiological projections indicate that in 2025, Brazil will have the sixth largest population of elderly people , on average 30 million people, which leads to an increasing number of HF cases and expenses with the disease (Mizzaci et al., 2017; Brasil, 2022).

Due to the important outcome related to mortality and decrease in quality of life, initially pharmacological therapies focused on the final components of this syndrome such as volume overload (congestion) and myocardial dysfunction (heart failure), emphasizing the use of diuretics and cardiac glycosides, which are effective drugs in relieving symptoms and stabilizing patients with hemodynamic decompensation. But these strategies did not change the outcome of gain in survival for the patient. The advancement of studies provided new knowledge and then, heart failure started to be observed as a consequence of a dynamic circulatory disorder and pathological cardiac remodeling. These advances have had a positive impact on the treatment of CHF and on the patient's quality of life (Tomasoni et al., 2019; Truby & Rogers, 2020).

1.2 Pharmacological Management

The pharmacological treatment of patients with HFrEF is based on the relief of congestion through the use of diuretics and on neurohormonal inhibition to improve the clinic status by reducing hospitalizations and mortality (Tomasoni et al., 2019).

The different pharmacological and non-pharmacological therapeutic strategies bring optimistic data regarding the

treatment of CHF, however, the results achieved in clinical studies are still not reproducible in the general population, since mortality, hospitalizations and re-hospitalization rates have not decreased significantly. The explain should be due to the fact that the results obtained from clinical trials are difficult to put into practice, due to problems related to patient adherence to treatment, the presence of comorbidities not represented in clinical trials and the tendency of the systems of health to acute illnesses, giving less attention to the continuous monitoring and therapeutic measures needed in chronic health conditions (Ferrante., 2011).

Data from the BREATHE (Brazilian Registry of Acute Heart Failure) showed that poor adherence by the patients combined with inadequate control of comorbidities such as arterial hypertension, diabetes and the persistence of neglected diseases such as Chagas disease (CD) are the causes of re-hospitalizations and high in-hospital mortality rate. Therapeutic decisions must be individualized to each clinical case and based on the stage of disease evolution. In addition, must be able to act in different ways, such as prevention of structural damage and the evolution of HF, symptomatic and palliative cares (Albuquerque et al., 2015).

Therefore, these therapeutic interventions can be made based on the ACC/AHA stage in order to modify risk factors (stage A), treat risk and structural heart disease to prevent HF (stage B) and reduce symptoms, morbidity and mortality (stages C and D) or by patient prognosis and response to treatment by LVEF or by symptoms evolution by NYAH classification (Heidenreich et al., 2022).

1.2.1 Diuretics

Diuretics are widely used to improve or decrease symptoms of fluid retention and congestion in patients with heart failure, because they promote diuresis and relief from volume overload through urinary Na+ excretion. However, the diuretic effects on morbidity and mortality are still known, therefore, it should not be used alone, but in combination with other drugs that prolong patient survival (Cai, 2000; Rohde et al., 2018).

The loop diuretic class is largely prescribed and is certainly the most potent class of diuretics available in clinical medicine. Among the outstanding drugs of this group, we have furosemide, which acts on the ascending limb of the loop of Henle, inhibiting the cotransporter responsible for the reabsorption of Na+/K+/2Cl-. In addition to these, the diuretics available in clinical practice are the thiazides such as hydrochlorothiazide, which act by preventing the reabsorption of Na+ and 2Cl- by blocking the membrane transport protein present in the distal convoluted tubule, and by the way these drugs increase diuresis (Rohde et al., 2018).

Not only the thiazide class but also the loop class of diuretics increase the excretion of Na+, K+, and H+ in the urine, causing hypokalemia and metabolic alkalosis. However, there are classes of diuretics that increase Na+ excretion but spare K+ and H+ and, therefore, cause hyperkalemia and metabolic acidosis. An example is the class of potassium-sparing diuretics, which the drug amiloride acts on the collecting tubules preventing the reabsorption of Na+ and the elimination of K+, as well as the drugs spirolactone and eplerenone, which act by antagonizing the mineralocorticoid receptors, located in the distal convoluted tubule, leading to elimination of Na+ and retention of K+ and H+ (Silva, 2010).

1.2.2 Angiotensin-converting Enzyme Inhibitors

Angiotensin-converting enzyme inhibitors (ACEi) are essential for the treatment of heart failure, since the use of this class of drugs by symptomatic patients has promoted several advantages, such as reduction of symptoms, improvement in quality of life and physical performance, decreased number of hospitalizations and reduced mortality. In asymptomatic patients with ventricular dysfunction, the clinical use of ACE inhibitors can prevent the onset of heart failure and stabilize LV remodeling (Barreto & Ramires, 1998; Rohde et al., 2018).

ACEi act by blocking the renin-angiotensin-aldosterone system, precisely by inhibiting the enzyme responsible for converting angiotensin I to angiotensin II, and the enzyme kininase II, a fact that leads to an increase in bradykinin, intensifying the effects of angiotensin suppression. Among the angiotensin-converting enzyme inhibitors are captopril, enalapril, ramipril, lisinopril and cilazapril (Silva, 2010; Yancy et al., 2013) .

1.2.3 Angiotensin II Receptor Blocker

For the functioning of the RAAS, renin is produced in the region of the juxtaglomerular apparatus and will be converted into angiotensin I, which is relatively inactive and subsequently undergoes the action of the angiotensin II-converting enzyme, to become the active form responsible for the elevation of blood pressure levels by secondary vasoconstriction to the direct action on the muscular layer of the vascular wall that increases myocardial contractility and stimulates the release of aldosterone in the adrenals. In addition, this sequence of activation could generate water retention and stimulate the secretion of catecholamines and the action of the sympathetic nervous system. (Filho, 2007).

The class of angiotensin receptor blocker (ARB) or angiotensin II antagonists is losartan, however, currently, there are many other drugs, such as valsartan, irbesartan and candesartan, which have already been tested in the context of heart failure. ARBs are an alternative with comparable efficacy to ACE inhibitors and are indicated for patients intolerant or with a documented allergy to this class of drugs, which is the case with persistent cough or the occurrence of angioedema (Rohde et al., 2018).

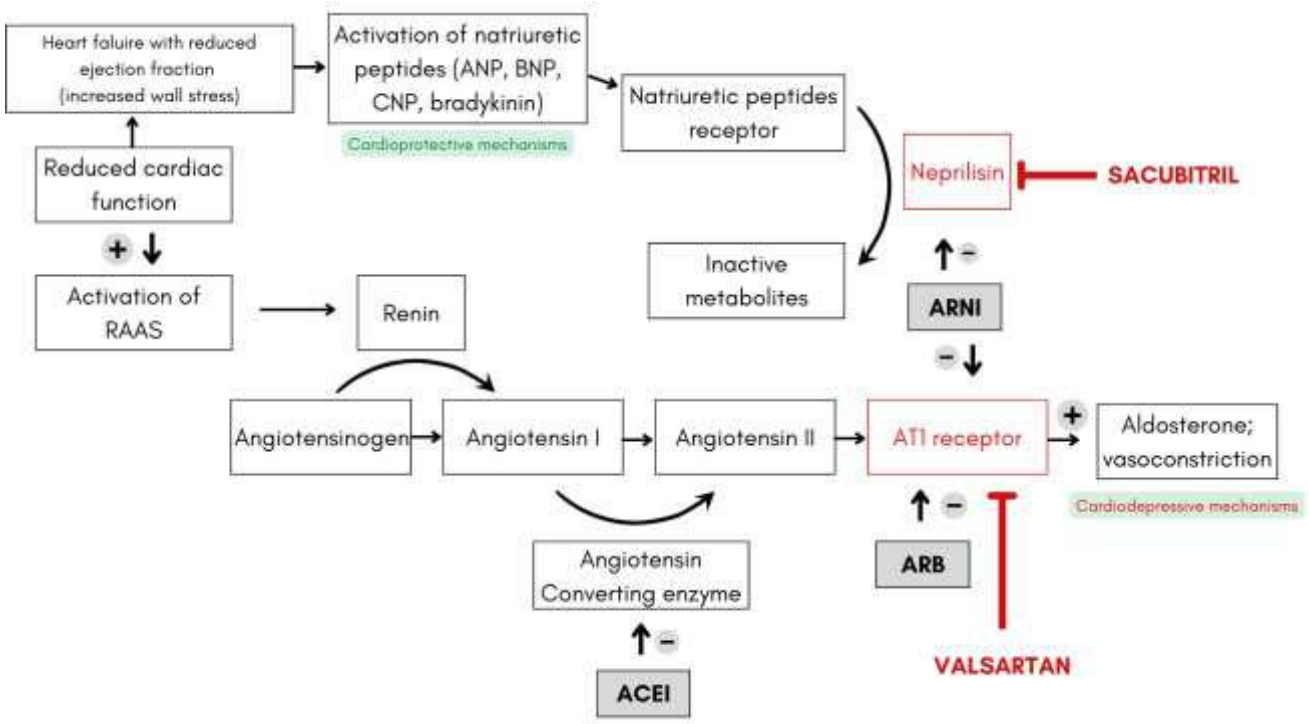
1.2.4 Angiotensin receptor-Neprilysin Inhibitor

Sacubitril/valsartan represents a new therapeutic class, which acts both on the RAAS and on neutral endopeptidase hence the name angiotensin receptor-neprilysin inhibitor (ARNI). This new alternative for the pharmacological treatment of HF combines the effects of inhibition of neprilysin through sacubitril, and blockade of the angiotensin II receptor type-1 (AT1) through valsartan (Figure 1). The neuromodulatory effects of ARNI are given by the combination of RAAS inhibition with the activation of beneficial and cardioprotective neurohormones, the natriuretic peptides, which exert vasodilation, natriuresis and diuresis effects, as well as anti-fibrotic, anti-hypertrophic and antioxidants (Burnett et al., 2017; Kuster & Pfister, 2019; Książczyk & Lelonek, 2020).

These data are from the PARADIGM-HF (Prospective Comparison of ANRI with ACEi to Determine Impact on Global Mortality and Morbidity in Heart Failure) clinical trial, which investigated the long-term effects of sacubitril/valsartan compared to enalapril (ACEi), on morbidity and mortality in patients with symptomatic and persistent HFrEF, on optimized clinical therapy, high levels of plasma natriuretic peptides and reduced creatinine clearance, which proved that ARNI therapy is superior to ACEi therapy due to the reduction in hospitalizations, disease decompensation, overall mortality, sudden death, and cardiovascular disease mortality, as well as representing a safer option for renal function (Rohde et al.. 2018; Schwinger, 2021).

It is worth notifying that oral neprilysin inhibitors associated with ACEi, can lead to higher frequency of angioedema, and because of this concomitant use is contraindicated and should be avoided (Heidenreich et al., 2022).

Figure 1 - Physiopathology of heart failure and pathways of activation RAAS, natriuretic peptide systems and points to action for ACEI, ARB, and ARNI in the neurohormonal cascade. *The ARNI valsartan/sacubitril combines traditional neurohormonal inhibition targeting the RAAS with an activation of beneficial neurohormones of the natriuretic peptide system through inhibition of natriuretic peptide degradation, thereby promoting their multiple effects. RAAS: renin-angiotensin-aldosterone system; AT1 receptor: angiotensin II type 1 receptor; ANP: atrial natriuretic peptide; BNP: brain natriuretic peptide; CNP: C-type natriuretic peptide; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor/neprilysin inhibitor; (see "+" for activation , "–" for inhibition and "curved arrow" for converting action).



Source: Adapted from Kuster, G. M., & Pfister, O. (2019). Chronic heart failure: advances in pharmacological treatment and future perspectives. Swiss medical weekly, 149, w20036.

1.2.5 Sodium-glucose Cotransporter 2 Inhibitor

Diabetes and HF are side by side, since HF leads to insulin resistance and, therefore, contributes to the development of diabetes and 30% of patients with diabetes have cardiac and ventricular dysfunction. Despite this, it is known that kidneys make an important functions in the regulation of glucose homeostasis, but recently the main glucose regulatory system in the kidney, glucose-spatter (target SGLT) and its isoforms SGLT1 and SGLT2, have become the mainstay of type 2 diabetes therapy (Kuster & Pfister, 2019).

The Sodium Glucose Cotransporter 2 Inhibitors (SGLT2i) are recommended to reduce HF and cardiovascular hospitalization, regardless of the presence of type 2 diabetes. To prove the efficacy of SGLT2i in the outcome of the patients of studies with HF in the absence of type 2 diabetes, the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial and EMPEROR-Reduced (EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction) showed the benefit of SGLT2i (dapagliflozin and empagliflozin, respectively) versus placebo on outcomes like reduced the cardiovascular death or HF hospitalization (Heidenreich et al., 2022).

1.2.6 β-adrenergic Receptor Antagonists

β-blockers (eg, bisoprolol, carvedilol, sustained-release metoprolol succinate) are also considered first-line drugs in the treatment of HFrEF because they reduce overall mortality, death from HF and sudden death, in addition to improving symptoms and reducing recurrence rates hospitalizations for HF (Marcondes-Braga et al, 2021). β-blockers can preserve myocardial structure and function due to the fact that they prevent the increase in the concentration of the cyclic AMP second messenger and the myocardial Ca2+ overload, as well as by decreasing the activation of Ca2+-dependent ATPase enzymes and, consequently, the reduction of highly energetic phosphates, resulting from the stimulation of adrenergic receptors (Batlouni & Albuquerque, 2000).

β-adrenergic blockade can decrease cardiac arrhythmias by reducing heart rate, improving ventricular function, reducing cardiac automaticity and preventing hypokalemia. The long-term use of β-blockers in patients with CHF induces important and beneficial effects such as, for example, an increase in left ventricular ejection fraction, a progressive reduction in left ventricular volumes and myocardial mass and reduces mitral regurgitation, which may reverse changes related to ventricular remodeling (Batlouni & Albuquerque, 2000).

Carvedilol has β-blocking properties plus an alpha-blocking action of antioxidant properties. The introduction to the treatment should be carried out after the patient has reached a period of partial compensation with the other interventions, it is recommended to start after the disappearance of lower limb edema. Bisoprolol and metoprolol are used with the same care applied to carvedilol (Silva, 2010). The cardioselective β-blockers, bisoprolol and metoprolol succinate, are indicated in patients with chronic obstructive pulmonary disease, diabetics on insulin treatment, and in patients with peripheral artery disease (Yancy et al., 2013).

In particular, with attention to the HFpEF, beta blockers may be used to treat hypertension in patients with a history of myocardial infarction, symptomatic coronary artery disease or atrial fibrillation with rapid ventricular response, but these effects need to be balanced with the potential contribution of chronotropic incompetence to exercise intolerance in some patients (Heidenreich et al., 2022).

1.2.7 Vasodilators

The association of nitrate and hydralazine was a strategy that showed beneficial effects on clinical outcomes in patients with heart failure. Studies have shown that there could be racial differences related to the efficacy of vasodilators used in the treatment of HF. The A-HeFT study (African-American Heart Failure Trial) showed that the association of nitrate with hydralazine improved the patient's quality of life and reduced the hospitalization rate by 33% and the total mortality rate in patients self-declared blacks in NYHA functional class III-IV, under optimized clinical treatment. See below in Graph 1. This association is also indicated, but with a lower level of recommendation, in case of worsening renal function and/or hyperkalemia with the use of ACEI/ARB (Rohde et al. 2018; Heidenreich et al., 2022).

Several vasodilator drugs currently used to treat HF promote vascular smooth muscle relaxation by increasing the concentration of nitric oxide (NO), a substance responsible to activating the soluble guanylate cyclase enzyme, which in turn increases the transformation of GTP on the second messenger cyclic GMP (cGMP), what activates cGMP-dependent protein kinases, promoting smooth muscle relaxation to next intracellular protein phosphorylation. NO acts as an intracellular and paracrine autacoid that, endogenously, is synthesized from arginine by NO synthase enzymes, found in endothelial cells and in the smooth muscle that constitutes the tunica media of the blood vessel wall. Nitrates are relatively safe and effective, as well as contributing to the treatment of patients with CHF because they reduce both left ventricular filling pressures and left ventricular ejection impedance and, therefore, improve the performance of ventricular function as well decrease the mitral and aortic insufficiency. These effects also promote increased cardiac output and improve renal perfusion, with increased urinary

output (Silva, 2010; Rohde et al., 2018).

Among the intravenous vasodilators, the highlight goes to sodium nitroprusside and intravenous nitroglycerin. Sodium nitroprusside is a mixed-action vasodilator (arteriolar and venous) used by venous infusion that has the donation of free NO as its mechanism of action, which promotes endothelium-independent muscle dilation. Venous nitroglycerin, on the other hand, has a more intense vasodilating property than sodium nitroprusside and is relatively selective for venous capacitance vessels, being more indicated for the treatment of left heart failure due to acute myocardial ischemia and non-ischemic left ventricular failure when required a rapid reduction in ventricular filling pressures (Silva, 2010).

Hydralazine, finally, acts as a direct arterial vasodilator, generating the relaxation of the smooth muscle of resistance arterioles and, therefore, causing a reduction in left ventricular afterload, increasing cardiac output and leading to reflex tachycardia (Silva, 2010).

1.2.8 Aldosterone Receptor Antagonist

Patients with CHF have a high level of aldosterone in their plasma, on average, up to 20 times of normal level. Aldosterone exerts several biological effects beyond to Na+ retention and, therefore, clinical use of aldosterone receptor antagonists may be beneficial for patients with HF (Silva, 2010).

These aldosterone receptor antagonist also known as Mineralocorticoid Receptor Antagonists (MRA) or anti mineralocorticoids, is recommended to reduce morbidity and mortality of the patients with HF, if eGFR is >30 mL/min/1.73 m2 and serum potassium is <5.0 mEq/L. Then, careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely monitored thereafter to minimize risk of hyperkalemia and renal insufficiency (Heidenreich et al., 2022).

Among the aldosterone receptor antagonists, we can highlight eplerenone, which has greater selectivity for aldosterone receptors, and spironolactone, which has lower specificity and, therefore, also blocks androgen receptors, which can occasionally result in adverse effects such as gynecomastia in 10% of male patients and vaginal bleeding. Spironolactone and eplerenone act by blocking the aldosterone receptor in the distal convoluted tubule, decreasing reabsorption and increasing excretion of Na+, and retention of H+ and K+. They also block the action of aldosterone on specific fibroblast receptors, reducing the production of type I collagen, which may decrease the myocardial remodeling process that occurs in CHF (Silva, 2010; Heidenreich et al., 2022).

1.2.9 Calcium Channel Blockers

Calcium channel blockers exhibit different pharmacological behaviors, depending on the site where they bind. Second-generation dihydropyridine calcium channel blockers, including amlodipine and felodipine, have greater selectivity for calcium channels in vascular smooth muscle cells and less myocardial depressant activity, unlike nondihydropyridine calcium channel blockers— diltiazem and verapamil— are myocardial depressants and generally not well tolerated in HF. By reducing peripheral vasoconstriction and LV afterload, calcium channel blockers were thought to have a potential role in the management of chronic HF (Heidenreich et al., 2022).

Since second generation dihydropyridine acts reducing peripheral vasoconstriction and LV afterload, calcium channel blockers were thought to have a potential role in the management of chronic HF, whereas PRAISE-2 (Prospective Randomized Amlodipine Survival Evaluation 2) trial, that enrolled only patients with nonischemic cardiomyopathy and no survival benefit was observed. Nowadays, in AHA/ACC/HFSA Heart Failure Guideline, dihydropyridine calcium channel-blocking and nondihydropyridine calcium channel-blocking drugs are not recommended treatment for HF, and the latter group being considered as may be harmful to patients with low LVEF, because of their negative inotropic effects. However, in cases of

patients with hypertension who still with elevated blood pressure despite optimization therapy, the dihydropyridine calcium channel blockers may be used (Tavares et al., 2017; Heidenreich et al., 2022).

1.2.10 Digitalis

Cardiotonic digitalis exert a moderate positive inotropic effect on cardiac muscle, through the competitive blockade of the Na+/K+ ATPase pump, by the digitalis bind on the K+ binding site. This blockade promotes an increase in intracellular Na+ concentration with a decrease in Ca2+ efflux, performed by the Na+/Ca2+ ATPase exchanger, located in the cardiomyocyte membrane. This increase in intracellular Na+ concentration leads to an enhancement in myocardial inotropism. In practice, the Digitalis Investigation Group (DIG) findings shows the serum digoxin concentration was directly related to mortality, because in patients with heart failure but not AF treated with low digoxin levels (between 0.5 and 0.8 ng/ml) had a reduced in mortality outcomes, but the mortality increases among patients with levels >1.1 ng/ml (Adams et al., 2016)

A meta-analysis on the studies available to date on digitalis in heart failure revealed that treatment with digoxin reduces hospitalizations and improves the symptoms of HF, but mortality was not affected by this treatment. So the current recommendation is that digoxin might be considered to decrease hospitalizations for HF in patients with symptomatic HFrEF despite optimization therapy or in patients unable to tolerate the triple therapy to reduce mortality. But the benefit of digoxin in patients with HF remains controversial (Berliner & Bauersachs, 2020).

1.2.11 Inotropes

Cardiac inotropes are used in patients with symptomatic hypotension, low cardiac output with organ dysfunction, or cardiogenic shock. Inotropes have the function of increasing the force of myocardial contraction to improve cardiac output, maintenance of perfusion pressure and adequate blood flow to the organs (Rohde et al., 2018).

Among the inotropic drugs, we can highlight β1-adrenoceptor agonists, phosphodiesterase enzyme inhibitors and calcium sensitizing agents. β1-adrenoceptor acts in a cascade reactions as agonists of the metabotropic receptors in the heart. Since these receptors are coupled to Gs proteins, they activate the enzyme adenylate cyclase, which transforms ATP into the second messenger cyclic AMP (cAMP). This second messenger, in turn, activates cAMP-dependent protein kinases, which carry out phosphorylation reactions of effector proteins, causing an increase in cytoplasmic Ca2+ and binding of this ion with the contractile proteins of cardiomyocytes, resulting in positive inotropism in the heart. On the other hand, phosphodiesterase inhibitor drugs reduce the degradation of cAMP performed, causing an increase in the intracellular concentration of this second messenger and, consequently, enhance in the strength of myocardial contraction. Finally, Ca2+ sensitizing drugs act by promoting positive inotropism without increasing the concentration of Ca2+ inside the cardiomyocyte, because these drugs stabilize the conformational changes of contractile proteins induced by Ca2+, increasing the possibility of interaction of the contractile proteins actin and myosin (Silva, 2010).

In general terms, reviews HF management, inotropes could be used as palliative care in patients with advanced (stage D) HF refractory optimized therapy recommended in guidelines as first line therapy, ensuring an improvement in organ dysfunction. But despite improving hemodynamic compromise, positive inotropic agents have not shown improved survival in HF patients (Rohde et al, 2018; Heidenreich et al., 2022).

Dobutamine, a positive inotropic agent, acts stimulating β1-adrenergic receptors, increasing the myocardial contractility, and on β2-adrenergic receptors of smooth muscle, causing vasodilation. By these factors, dobutamine is widely used in the treatment of HF due to its ability to increase cardiac output and reduce left ventricular filling pressures (Amado et al., 2016).

In addition, dopamine is a natural precursor of noradrenaline and adrenaline, with a dose-dependent effect. By this

way, the dopamine at low doses, has vasodilating effects after binding and activating its receptors, however, at high doses this drug promotes the activation of β1-adrenergic receptors and, when administered in very high doses, dopamine acts as an agonist of α1-adrenergic receptors, causing vasoconstriction and increased blood pressure (Amado et al., 2016).

Milrinone is a bipyridine derivative that acts by promoting inhibition of the phosphodiesterase-3 enzyme, which is responsible for the degradation of cAMP in the myocardium and in the vascular smooth muscle. It results in a gain of intracellular cAMP and, consequently, improvement of myocardial contractility and adequate arterial and venous vasodilation with a consequent drop in systemic and pulmonary vascular resistance, as well as in the filling pressure of the left and right sides of the heart. In summary, cardiac output increases due to stimulation of myocardial contractility and reduction of left ventricular afterload (Silva, 2010; Heidenreich et al., 2022).

Levosimendan, other inotropic drug, acts through two mechanisms of action: increased troponin and intracellular sensitivity for Ca2+ and activation of K+ channel ATP dependent, resulting in muscle and vascular relaxation, consequently, peripheral coronary vasodilation (Amado, 2016). Furthermore, noradrenaline is indicated in patients with severe hypotension or cardiogenic shock, or in the presence of systemic inflammation associated with acute HF. (Rohde et al., 2018).

1.2.12 Antiarrhythmics

As known, atrial fibrillation (AF) is the most common arrhythmia in HF patients and it leads to an increased risk of thromboembolic events such as ischemic stroke and exacerbation of HF symptoms. Another common occurrence in patients with HF is ventricular arrhythmias, that may be a source of precordial symptoms, sudden death and ventricular dysfunction. Antiarrhythmics can be used to supply ectopic ventricular rhythms in patients with HF. However, this kind of drug is not recommended for patients with asymptomatic or non-sustained ventricular arrhythmias (Heidenreich et al., 2022).

Therefore, the use of antiarrhythmic drugs should be considered in patients with incessant sustained ventricular tachycardia, ventricular fibrillation, sudden death resuscitation, recurrent or sustained atrial arrhythmias associated with symptoms or high ventricular response. Amiodarone, a representative of antiarrhythmics, is not recommended for patients with CHF already treated with drugs that reduce the mortality and, beside this, recent trials show that ablation may be preferable to antiarrhythmic drugs for a rhythm control strategy (Cai, 2001; Rohde et al., 2018; Heidenreich et al., 2022).

1.2.13 Anticoagulants

HF could be considered as a hypercoagulable state and as an independent risk factor for stroke, systemic embolism, and mortality in the setting of AF, because of this it is recommended to receive chronic anticoagulant therapy (Rohde et al., 2018).

One of the most used drugs is warfarin, that is associated with a reduction in major cardiovascular events and death in patients with HF in some studies, but the risk of thromboembolic events was not lower in patients with HF taking warfarin than in patients not treated with antithrombotic drugs and there was a significant increase in major bleeding. Likely, a trial of rivaroxaban in patients with HFrEF, coronary artery disease (CAD) and normal sinus rhythm showed no difference in mortality, MI, and stroke compared with placebo. Therefore, contrary to what was thought there is no evidence of benefit for anticoagulation in HF patients without a specific indication (eg, AF, a previous thromboembolic event, or a cardioembolic source) (Heidenreich et al., 2022).

1.2.14 I_f inhibitors

At last, the inhibitors of funny current (If) in sinoatrial nodal tissue, also acts as negative chronotropic agent. This inhibition is selective, different from other negative chronotropic agents. Due to the fact, sinoatrial nodal is unique cells with

an innate ability to generate a cyclical change in their resting membrane potential, reaching the threshold needed for spontaneous depolarization (Koruth et al., 2017).

The major representative of this group is ivabradine, thus pharmacological mechanisms result in a decrease in the rate of diastolic depolarization and, consequently, the heart rate. The efficacy of ivabradine was demonstrated by reducing the composite endpoint of cardiovascular death or hospitalization for HF in patients with HF. Nowadays, aiming to reduce the HF hospitalizations and cardiovascular death, a lower heart rate is beneficial to HF patients, so ivabradine is recommended for patients with symptomatic (NYHA class II to III) stable chronic HFrEF with adequate treatment, including a beta blocker at maximum tolerated dose and sinus rhythm with a heart rate of ≥70 bpm at rest (Heidenreich et al., 2022).

2. Methodology

A selective literature search was conducted in an international database (PubMed) carried out in the following stages: establishment of the research question; search for primary studies; data extraction from primary studies; evaluation of primary studies included in the review; analysis and synthesis of the review results; assessment of methodological quality and presentation of results.

The inclusion c were the articles that contemplated the proposed theme, while the exclusion criteria were duplicate articles, which dealt with studies in very delimited and specific populations or that did not fit the proposed objective, but were not opposed to it. Original articles were included, with no temporal delimitation for the searches, published in English, Portuguese and Spanish. It is noteworthy that all pertinent guidelines were considered.

3. Results and Discussion

Persistent activation of the sympathetic nervous system and renin-angiotensin-aldosterone system compose the basis of HF. The increase in the performance of the heart, as a compensation mechanism, in the face of various stressors was initially beneficial to the body, but in the long term, starts the cardiac remodeling and the progression of chronicity of the disease (Książczyk & Lelonek, 2020).

Inhibition of the renin-angiotensin-aldosterone system is recommended to reduce morbidity and mortality in patients with HFrEF, and current guideline shows that the activation of natriuretic peptides has benefits in these patients outcome. Then, ACEi or ARB, beta blockers, MRA and SGLT2i are recommended as first-line therapy such as shown on Table 1 (Tomasoni, 2019;Heidenreich et al., 2022).

Pharmacological therapy to reduce morbidity and mortality in HF and recommended for many years was based on inhibition of the RAAS with the ACEi or ARB. Although, PARADIGM-HF trial showed major benefits with sacubitril/valsartan when compared to enalapril. Besides, PIONEER-HF trial showed that ARNi reduced NT-proBNP levels in patients hospitalized for acute decompensated HF without increased rates of adverse events like worsening renal function, hyperkalemia and symptomatic hypotension when compared with enalapril (Heidenreich et al., 2022).

The MRA therapy shows consistent benefits in all-cause mortality, HF hospitalizations, and sudden cardiac death of patients with HFrEF. However, are necessary regular checks of serum potassium levels and renal function approximately 1 week, then 4 weeks, then every 6 months after initiating or intensifying MRA. In case of clinical instability, increase testing frequency as needed (Heidenreich et al., 2022).

To relieve the symptoms the highlight goes to diuretics such as furosemide, whose goal use is to eliminate clinical evidence of fluid retention. Except the MRA, diuretics treatment is still uncertain to reduce morbidity and mortality outcome. During the treatment, hyponatremia may develop, which complicates HF management. Then, the use of diuretics are

recommended at the lowest dose possible to maintain euvolemia for HFpEF patients associated with non-pharmacological strategies, such as management of hypertension, obesity and coronary artery disease. Vasopressin antagonists could be helpful as pharmacological strategies to improve hyponatremia and decrease congestion while maintaining serum sodium (Heidenreich et al., 2022).

In addition to these, vasodilators like nitrate and hydralazine and inotropic drugs such as dobutamine are also used to relieve symptoms. Anticoagulants and antiarrhythmics are recommended only in specific clinic cases. Nonetheless, digoxin and calcium channel blockers have not shown improved survival in HF patients or be harmful to patients. The recommendation of digoxin is still unclear in some specific cases as patients are unable to use first line therapy recommended by guideline. However this drug needs close monitoring due to occurrence of digitalis intoxication (Wu et al., 2021).

Nondihydropyridine calcium channel blockers—diltiazem and verapamil—are myocardial depressants and generally not well tolerated in HF. Verapamil had no impact on survival or major cardiac events post-MI, including in those patients with HFrEF after acute MI. Dihydropyridine calcium channel blockers, including amlodipine and felodipine have no conclusion effects with nonischemic cardiomyopathy, no survival benefit was observed. indicating the limitations of conclusions derived from subgroup analyses. Finally, ivabradine despite not reduce (Heidenreich et al., 2022).

Table 1 - Summarized pharmacological treatment for Heart FailurenACEI indicates: angiotensin converting enzymes inhibition; ACE: angiotensin converting enzymes; AT1: angiotensin 1 receptor; RAAS: renin-angiotensin-aldosterone system; HF: heart failure; HFrEF: heart failure with reduced ejection of fraction; ARB: angiotensin receptor blocker; DCT: distal convoluting tubule; ANRI: Angiotensin neprilysin receptor inhibitor; LV: left ventricle; NYAH: New York Heart Association classification; eGFR: estimated glomerular filtration rate; PDE: phosphodiesterase; CV: cardiovascular.

Drug Therapy (eg,)	**Recommendation**	**Mechanism**	**Clinical outcome**	**Adverse effect**
Diuretics (- loop: furosemide, bumetanide, torsemide); (- thiazide and thiazide-like: chlorthalidone, hydrochlorothiazide); (- potassium-sparing diuretics: spironolactone)	Decompensated and congested HF patients; Thiazides in patients with poor response to increasing doses of loop diuretic.	Loop diuretic: inibem a reabsorção de Na+/K+/2Cl- na alça de Henle Thiazide: inibem a reabsorção de Na+ e $2Cl^-$ no DCT Potassium-sparing diuretics:	Congestion relief; symptomatic improvement	Hyponatremia; hypokalemia; worsening renal function; mortality.
ACEi (eg captopril, enalapril)	patients with HFrEF and asymptomatic patients with ventricular disfunction (stage B)	RAAS Inhibition by the inhibition of ACE	Quality of life improvement; reduces preview or current symptoms of chronic HFrEF; Prevent HF and reduce mortality in asymptomatic patients	Intolerable cough; Angioedema.
ARB (losartan, valsartan)	Reduce morbidity and mortality of HF patients with ACEi intolerances (intolerable cough/ angioedema)	RAAS Inhibition by the inhibition of AT1 receptor	Quality of life improvement; reduces preview or current symptoms of chronic HFrEF	Angioedema
ARNI (sacubitril/ Valsartan)	NYAH class II to IV patients; NYHA class II or III symptoms and they	RAAS Inhibition and activation of Natriuretic peptides by the Inhibition	De novo treatment in hospitalized patients, improvement in health	Angioedema; Symptomatic hypotension

	tolerate an ACEi or ARB	of AT1 receptor and of neprilysin	status, reduction morbidity and mortality in HFrEF and in the prognostic biomarker NT-proBNP, improvement of LV remodeling	
MRA (eplerenone, spironolactone)	NYHA class II to IV patients, if eGFR is >30 mL/min/1.73 m^2 and serum potassium is <5.0 mEq/L	Aldosterone antagonists	Patients with HFrEF, with current or previous symptoms	Hyperkalemia; Worsening of renal function; Renal insufficiency; Gynecomastia; Vaginal bleeding.
Beta Blockers (bisoprolol, carvedilol, metoprolol succinate)	Patients with HFrEF, with current or previous symptoms; after myocardial infarction	Inotropic and chronotropic negative activity	Reduces the risk of death and hospitalization in patients with HFrEF.	Bradycardia; worsening of HF symptoms
SGLT2i (dapagliflozin and empagliflozin)	Patients with symptomatic chronic HFrEF, independent of the presence of DM2	But the benefit appears independent of the glucose lowering effects.	Reduces the composite of cardiovascular death or HF hospitalization	Risk for genital infections; Risk for soft tissues infections; Euglycemic ketoacidosis.
Hydralazine and Isosorbide Dinitrate	To patients self-identified as African American with NYHA class III-IV HFrEF who are receiving optimal medical therapy* or in patients with current or previous symptomatic HFrEF with intolerances to first-line agents, such as ARNi, ACEi, or ARB, because of drug intolerance or renal insufficiency**	Vasodilation therapy	Improve symptoms and reduce morbidity and mortality	Taquycardia; Syncope; Drug interactions and adverse drug reactions.
Calcium channel blockers eg, amlodipine, felodipine, diltiazem and verapamil	Not recommended to patients with HFrEF or LVEF <50%; Patients with elevated blood pressure who have optimized treatment for hypertension.	Blocked calcium channels in vascular smooth muscle cells.	Myocardial depressants; Reduction peripheral vasoconstriction and LV afterload	Nondihydropyridine may causes negative inotropic effects; Fluid retention; Worse patients survival, except amiodarone and .dofetilide.
Digitalis eg, digoxin	Symptomatic HFrEF patients despite treatment or who are unable to tolerate the HF treatment	Antiadrenergic or provagal agent	Positive inotropic effects; Decrease HF hospitalization	Toxicity; Arrhythmias; Increased mortality.
Inotropes (eg, dopamine, dobutamine, milrinone, or norepinephrine)	As “bridge therapy” for HF advanced refractory to first line therapy and waiting for cardiac transplantation; HF patients who are refractory to other therapies and with end-organ hypoperfusion	Adrenergic agonists; PDE 3 inhibitor and Vasopressors	Positive inotropic effects; Maintain systemic perfusion and preserve end-organ performance	Tachyphylaxis; Tachyarrhythmias; Hypotension.

Antiarrhythmic	In patients with HFrEF, class IC antiarrhythmic medications are not recommended	Rhythm control	Rhythm control; Amiodarone and dofetilide exerce neutral effects on mortality in patients with HFrEF;	Increase the risk of mortality (class IV); Negative inotropic effects (Francis et al, 2014)
Anticoagulants (eg, aspirin, warfarin, or clopidogrel)	HF with permanent-persistent-paroxysmal AF, CV risk, previous thromboembolic event.	Acts at different sites of the coagulation cascade	Reduction in major cardiovascular events and death in patients with HF	Thromboembolic event; Bleeding events
Ivabradine	Symptomatic patients in NYHA class II to III stable chronic HFrEF (LVEF ≤35%) with beta blocker therapy at maximum tolerated dose, and who are in sinus rhythm with a heart rate of ≥70 bpm.	Inhibition of funny current (I_f) in sinoatrial nodal tissue	Reduce the heart rate	Bradycardia; dizziness or fatigue; prolonged QT interval

*These data indicates the A-HeFT (African-American Heart Failure Trial)
** According to Heidenreich et a, 2022, to analyze the second group of indicative patients the classification of this recommendation is 2b (weak) and the level of evidence is C-LD, ie, with limited data.
Source: The authors, 2022.

4. Conclusion

Heart failure (HF) remains a major cause of mortality, morbidity, and poor quality of life and therefore, performing the accurate and early diagnosis becomes an important factor to the patient outcome. Besides, the appropriate and effective pharmacological and non-pharmacological treatments provided a better quality of life and a reduction of hospitalizations and mortality rates. This article is aimed to give an update on recent advances in pharmacological management of this syndrome.
It results the knowledge that blocking RAAS and sympathetic nervous system and activating of natriuretic peptides, which exercise cardioprotective and hemodynamic effects

After results of PARADIGM-HF, Sacubitril/valsartan is indicated as a substitute to ACEi/ARBs in patients with HFrEF with NYHA class II or III symptoms and because of improvement in morbidity and mortality. It is worth notifying that mortality-reducing pharmacotherapy in HF currently includes ANRi, beta-blockers, MRA and SGLT2i. The present challenge is to transform the results achieved in clinical studies into reality for the majority of patients with HF. This goal will be achieved multidisciplinary care starts to be tangibility with prevention of the advancement of structural damage, promotion onset of symptoms and improvement survival and quality of life to patients with HF. Then, this route must be promoted through multidisciplinary care with improved access to recommended drugs, close monitoring of patients, healthy habits, control of comorbidities and therapeutic adherence.

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