DEPARTAMENTO DE INSUFICIÊNCIA CARDÍACA
DEIC
SBC

ABC Heart Failure & Cardiomyopathy

Volume 02 | Number 01

January/February/March 2022

Brazilian Society of Cardiology
ISSN-2764-3107

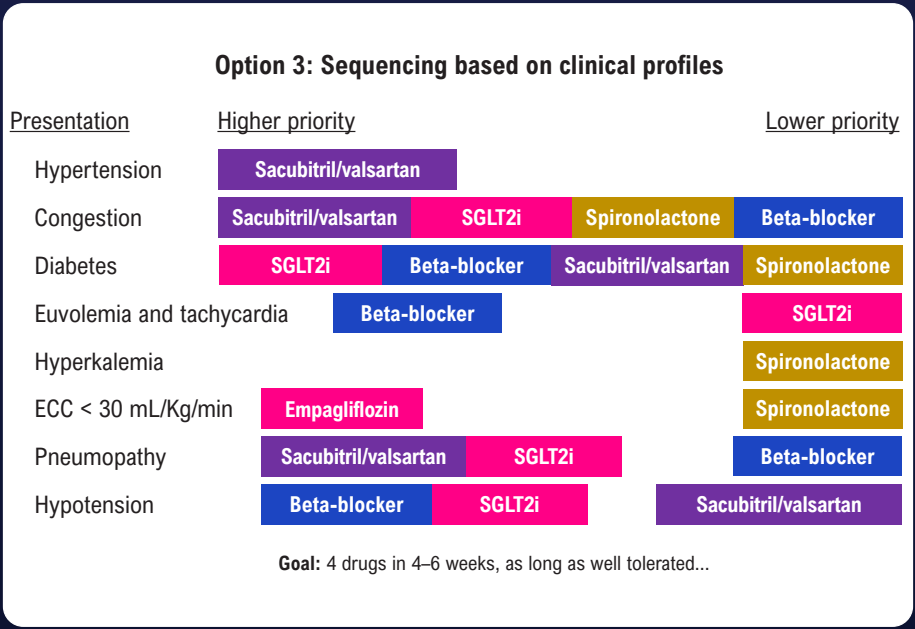


Figure 3, page 39

DEPARTAMENTO DE INSUFICIÊNCIA CARDÍACA
DEIC
SBC
ABC Heart Failure & Cardiomyopathy

Contents

DEPARTAMENTO DE INSUFICIÊNCIA CARDÍACA
DEIC
SBC

ABC
Heart Failure &
Cardiomyopathy

Administrative Council – Mandate 2022 (Brazilian Society of Cardiology)

North/Northeast Region
Nivaldo Menezes Filgueiras Filho (BA)
Sérgio Tavares Montenegro (PE)

Eastern Region
Denilson Campos de Albuquerque (RJ)
Andréa Araujo Brandão (RJ) – Vice-presidente do Conselho Administrativo

Região Paulista
Celso Amodeo (SP)
João Fernando Monteiro Ferreira (SP) – Presidente do Conselho Administrativo

Central Region
Carlos Eduardo de Souza Miranda (MG)
Weimar Kunz Sebba Barroso de Souza (GO)

South Region
Paulo Ricardo Avancini Caramori (RS)
Gerson Luiz Bredt Júnior (PR)

Editor-in-Chief of the ABC Cardiol (2022-2025)
Carlos Eduardo Rochitte

Editor-in-Chief of the IJCS (2022-2025)
Claudio Tinoco Mesquita

Presidents of State and Regional Brazilian Societies of Cardiology

SBC/AL – Pedro Henrique Oliveira de Albuquerque

SBC/BA – Joberto Pinheiro Sena

SBC/DF – Fausto Stauffer Junqueira de Souza

SBC/ES – Tatiane Mascarenhas Santiago Emerich

SBC/GO – Humberto Graner Moreira

SBC/MA – Francisco de Assis Amorim de Aguiar Filho

SBC/MG – Antônio Fernandino de Castro Bahia Neto

SBC/MS – Mauro Rogério de Barros Wanderley Júnior

SBC/NNE – José Albuquerque de Figueiredo Neto

SBC/PB – Guilherme Veras Mascena

SBC/PE – Carlos Japhet Da Matta Albuquerque

SBC/PI – Jônatas Melo Neto

SBC/PR – Olímpio R. França Neto

SOCERJ – Ronaldo de Souza Leão Lima

SBC/RN – Antônio Amorim de Araújo Filho

SOCERGS – Fábio Cañellas Moreira

SOCESP – Ieda Biscegli Jatene

Presidents of the Specialized Departaments and Study Groups

SBC/DA – Marcelo Heitor Vieira Assad

SBC/DCC – Bruno Caramelli

SBC/DCC/CP – Cristiane Nunes Martins

SBC/DCM – Maria Cristina Costa de Almeida

SBC/DECAGE – José Carlos da Costa Zanon

SBC/DEIC – Mucio Tavares de Oliveira Junior

SBC/DEMCA – Álvaro Avezum Junior

SBC/DERC – Ricardo Quental Coutinho

SBC/DFCVR – Elmiro Santos Resende

SBC/DHA – Lucélia Batista Neves Cunha Magalhães

SBC/DIC – André Luiz Cerqueira de Almeida

SBCCV – João Carlos Ferreira Leal

SOBRAC – Fatima Dumas Cintra
SBHCI – Ricardo Alves da Costa

DCC/GECIP – Marcelo Luiz da Silva Bandeira

DCC/GECOP – Maria Verônica Câmara dos Santos

DCC/GEPREVIA – Isabel Cristina Britto Guimarães

DCC/GAPO – Luciana Savoy Fornari

DCC/GEAT – Carlos Vicente Serrano Junior

DCC/GECETI – João Luiz Fernandes Petriz

DCC/GEDORAC – Sandra Marques e Silva

DCC/GEECG – Nelson Samesima

DCC/GERTC – Adriano Camargo de Castro Carneiro

DEIC/GEICPED – Estela Azeka

DEIC/GEMIC – Marcus Vinicius Simões

DEIC/GETAC – Silvia Moreira Ayub Ferreira

DERC/GECESP – Marconi Gomes da Silva

DERC/GECN – Lara Cristiane Terra Ferreira Carreira

DERC/GERCPM – Pablo Marino Corrêa Nascimento

ABC Heart Failure & Cardiomyopathy

Volume 2, Nº 1, January/February/March 2022

Address: Av. Marechal Câmara, 160 - 3º andar - Sala 330
20020-907 • Centro • Rio de Janeiro, RJ • Brasil
Phone.: (21) 3478-2700
E-mail: arquivos@cardiol.br
http://abccardiol.org/
SciELO: www.scielo.br

Commercial Department
Phone: (11) 3411-5500
E-mail: comercialsp@cardiol.br

Editorial Production
SBC - Internal Publication Department

Graphic Design and Diagramming
SBC - Internal Design Department

New Universal Definition of Heart Failure: A New Vision for Treatment

Evandro Tinoco Mesquita,[1,2,3,4] *Ana Paula Chedid,*[3,5] *Lidia Ana Zytynski Moura*[6]

Departamento de Insuficiência Cardíaca (DEIC),[1] *Rio de Janeiro, RJ – Brazil*
Sociedade Interamericana de Cardiologia (SIAC),[2] *Mexico*
Universidade Federal Fluminense,[3] *Niterói, RJ – Brazil*
Instituto Cardiovascular CHN/DASA e PROCEPI,[4] *Niterói, RJ – Brazil*
Santa Casa de Misericórdia do Rio de Janeiro,[5] *Rio de Janeiro, RJ – Brazil*
Pontifícia Universidade Católica do Paraná,[6] *Curitiba, PR – Brazil*

In March 2021, a new universal definition and classification for heart failure (HF) was published simultaneously in the *Journal of Cardiac Failure* and the *European Journal of Heart Failure*.[1] This document was produced by the European, North American, and Japanese Heart Failure Societies and was endorsed by the Canadian, Indian, Chinese, Australian, and New Zealand HF Societies. The objectives of the publication were to provide a universal, simple, and comprehensive **definition** that can guarantee standardization in clinical research, guidelines, and treatment, as well as guidance for patients and public policy makers. It also proposed a revised **classification** based on left ventricular ejection fraction (LVEF) to guide therapy according to HF category, and, finally, to revise the HF stages, aiming at both prognosis and prevention.

HF has been defined in Cardiology textbooks as a clinical syndrome characterized by the heart's inability to pump enough blood to meet the body's metabolic demands. However, this pathophysiological profile is only found in advanced stages of HF. Definitions vary in the guidelines of different Societies and also diverge from textbooks, including the concept of signs and symptoms associated with hemodynamic and neurohormonal abnormalities, which are neither simple nor easily measurable.

The new definition is comprehensive, unifying and facilitating the recognition of HF, incorporating not only signs and symptoms, but also objective markers of dysfunction and congestion. According to the new definition, HF is a clinical syndrome with signs and symptoms caused by a functional or structural cardiac abnormality that is accompanied by elevated natriuretic peptide levels and/or evidence of pulmonary or systemic congestion (Figure 1). The signs and symptoms cited in the document have been expanded and divided into typical and atypical. In addition, cut-off values for natriuretic peptides have been incorporated for the first time, as well as a list of situations that could influence them. This is an important point, since these biomarkers can accurately confirm or exclude the syndrome and make diagnosis easier and more objective.

Keywords

Heart Failure; Public Health; Family Medicine; Cardiomyopathies.

Mailing Address: Evandro Tinoco Mesquita •
Hospital Universitário Antônio Pedro
R. Marquês de Paraná, 303. Postal Code: 24033-900, Centro, Niterói, RJ – Brazil.
E-mail: etmesquita@gmail.com

DOI: https://doi.org/10.36660/abchf.20220001

The new classification according to LVEF allows the construction of a phenotype to guide treatment. Replacing the term "mid-range" with "slightly reduced EF" is noteworthy since current data show that neurohormonal blockade benefits this group of patients, as it does patients with HF with reduced EF (HFrEF).[2] Another important point that the new definition calls attention to is the clinical course of LVEF: LVEF in patients with HFrEF can be improved with optimized management. Moreover, an accelerated decline in EF indicates a need to intensify therapy.

HFrEF: HF with LVEF ≤ 40 %.

HF with slightly reduced **EF:** HF with LVEF 41-49%.

HF with preserved EF: HF with LVEF ≥ 50%.

HF with improved EF: HF with a baseline LVEF ≤ 40%, a ≥ 10 point increase from baseline LVEF, and a second measurement of LVEF > 40%.

Another important aspect was the revision of HF stages: At-risk for HF (stage A), Pre-HF (stage B), HF (stage C), and Advanced HF (stage D) (Figure 2). The terms "asymptomatic", "at-risk", and "pre-HF" will more convincingly describe the syndrome's severity to patients, thus reinforcing prevention and treatment adherence like the concept of pre-malignancy. It is also important that biomarkers (natriuretic peptides or troponin for those exposed to cardiotoxic agents) were added as an alternative to functional or structural change in stage B.

Another important innovation is the terminology used to describe the patient's clinical course: **worsening HF** (deterioration of signs and symptoms despite progression in therapy, requiring hospitalization or advanced intravenous therapy), **persistent HF** (lack of symptom improvement), and **HF in remission** (resolution of signs and symptoms accompanied by resolution of previous cardiac abnormalities). The results of the TRED-HF trial revealed that 40% of the dilated cardiomyopathy patients who had reverse remodeling and symptom improvement with treatment relapsed upon discontinuing therapy, which suggests remission rather than recovery.[3] Another prominent substitution was changing "stable HF" to "persistent HF", which highlights the concept of time-sensitive therapy to avoid therapeutic inertia (Figure 2).

The new definition is, in our view, an important milestone for standardizing diagnosis, understanding the syndrome's clinical course, and facilitating communication with patients who experience HF on a daily basis. The Brazilian Cardiology Society's Department of Heart Failure recommends this new approach that will be progressively incorporated into care and research (Figure 3).

Editorial

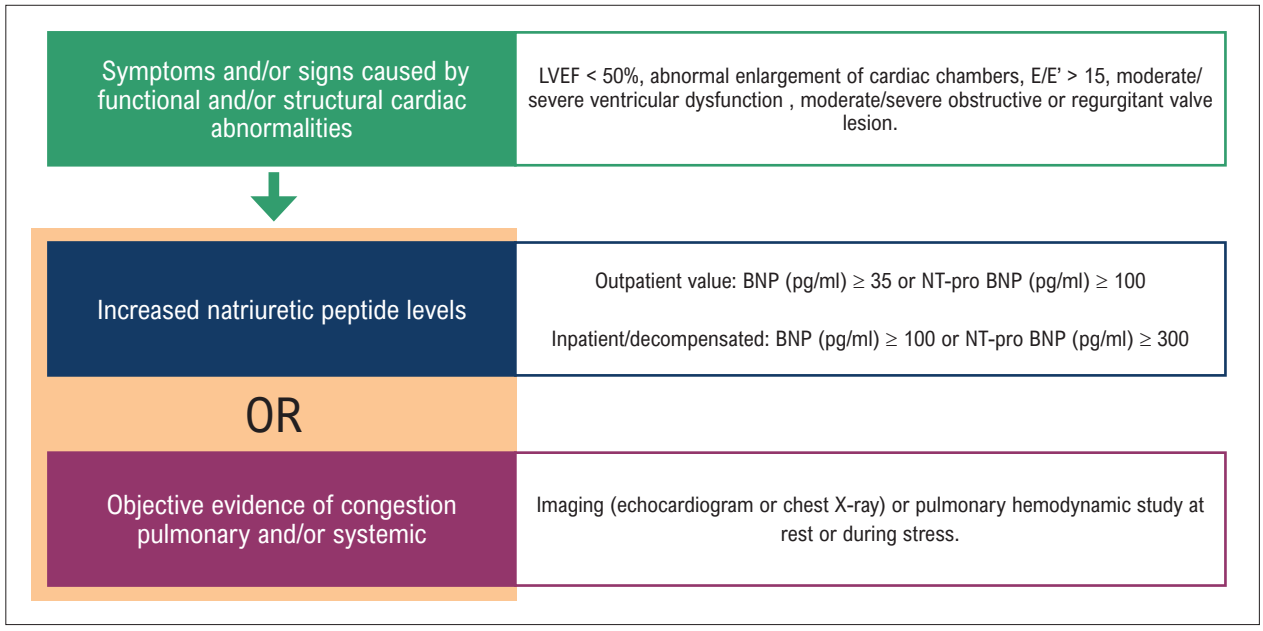


Figure 1 – *New universal definition of HF. LVEF: left ventricular ejection fraction; NT-pro BNP: N-terminal-pro B-type natriuretic peptide; E/E': ratio between early mitral inflow velocity and mitral annular early diastolic velocity. (modified from reference 1).*

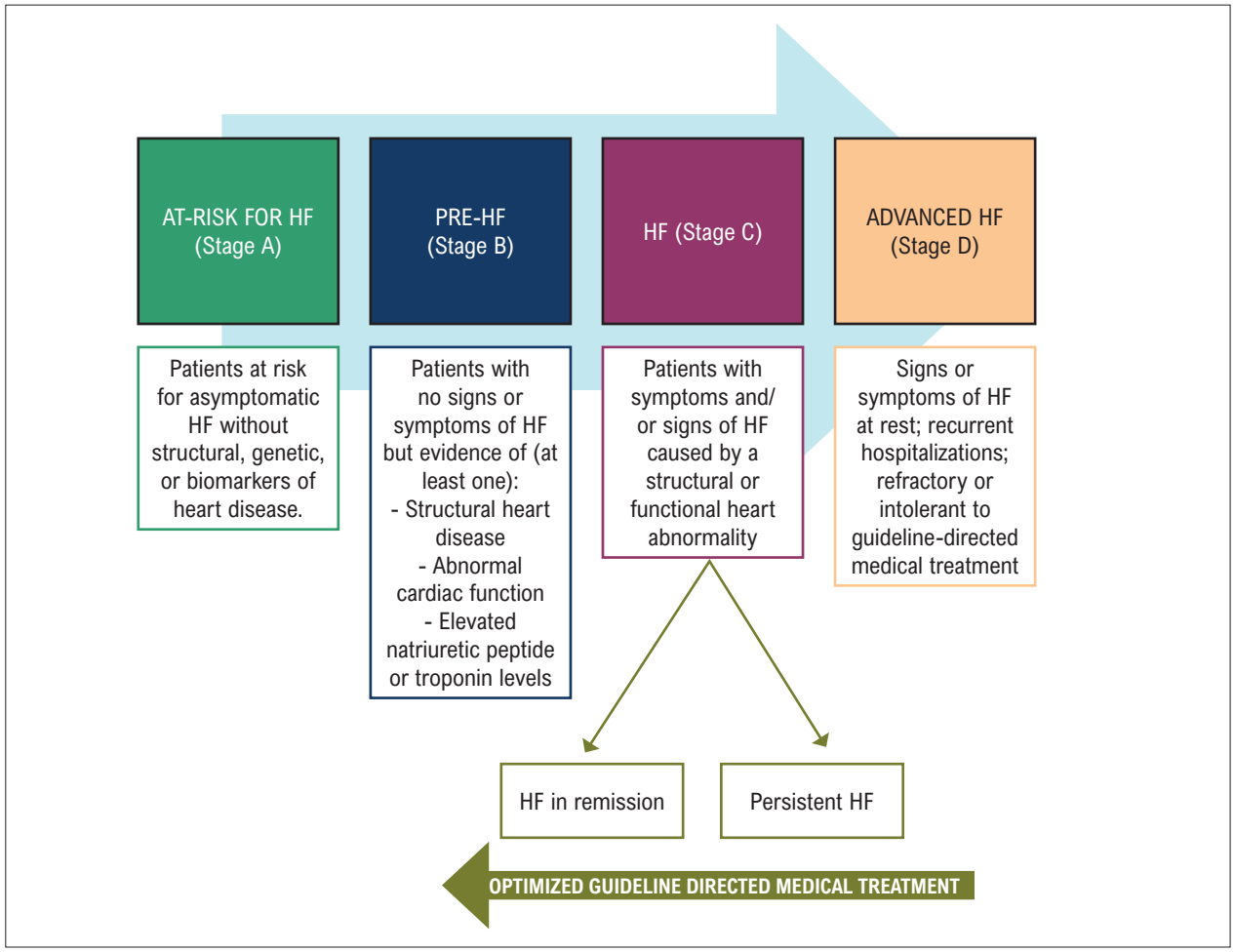


Figure 2 – *Stages in the development and progression of heart failure (HF). (modified from reference 1).*

Figure 3 – *Carlos Chagas - Day of the alert.*

References

1. Bozkurt B, Coats A, Tsutsui H. Universal Definition and Classification of Heart Failure. J Card Fail. 2021:S1071-9164(21)00050-6. doi: 10.1016/j.cardfail.2021.01.022.
2. Marcondes-Braga FG, Moura LAZ, Issa VS, Vieira JL, Rohde LE, Simões MV, et al. Emerging Topics Update of the Brazilian Heart Failure Guideline - 2021. Arq Bras Cardiol. 2021;116(6):1174-212. doi: 10.36660/abc.20210367.
3. Halliday BP, Wassall R, Lota AS, Khalique Z, Gregson J, Newsome S, et al. Withdrawal of Pharmacological Treatment for Heart Failure in Patients with Recovered Dilated Cardiomyopathy (TRED-HF): An Open-Label, Pilot, Randomised Trial. Lancet. 2019;393(10166):61-73. doi: 10.1016/S0140-6736(18)32484-X.

Review Article

Pharmacokinetics, Mechanism of Action, and Adverse Effects of the Main Drugs Used to Treat Heart Failure: A Practical Overview for the Clinical Cardiologist

Viviane Melo e Silva de Figueiredo,[1] João Vitor Soares Santos,[2] Bruna Costa de Albuquerque Bogéa,[1] Amanda Gomes de Oliveira,[1] José Albuquerque de Figueiredo Neto[1]

Universidade Federal do Maranhão,[1] São Luís, MA – Brazil

Universidade Estadual do Maranhão (UEMA),[2] Caxias, MA – Brazil

Angiotensin-converting enzyme inhibitors (ACEI)

Mechanism of action

The renin-angiotensin-aldosterone system (RAAS), and particularly angiotensin II, plays a crucial role in the pathophysiology of Heart Failure (HF), perpetuating cardiac remodeling, both on the cardiac structure level (provoking myocyte and fibroblast cell proliferation) and on the preload level (because of sodium retention and increased intravascular volume in the circulation), and in peripheral vascular resistance, by stimulating direct vasoconstriction and increased sympathetic discharge.[1]

As the name of the ACEI class implies, these drugs act to inhibit angiotensin-converting enzymes (ACEs) I and II, blocking the effects described above. This drug class also has an additional effect; ACE acts on a range of different substrates, including inactivation of bradykinin and other vasodilator peptides, and when this inactivation effect is blocked, there is an additional effect, reducing afterload.[2]

Pharmacokinetics

The ACEIs achieve bioavailability either in the form of the drug itself or as a pro-drug, depending on which pharmaceutical is chosen. In general, their metabolization is hepatic, but liver dysfunctions do not cause significant changes to their activation.[2] However, creatinine clearance abnormalities may preclude their use because they are excreted via this pathway and can contribute to maintenance of renal dysfunction.[1]

Enalapril is the principal member of this group used to treat HF. Its active metabolite is enalaprilat, which achieves maximum concentration 3 to 4 hours after administration and has a plasma half-life of around 11h. The maximum recommended dose of this medication is 40mg per day. It is recommended that enalapril should be introduced gradually and increased in accordance with the patient's tolerance, both in terms of symptoms of hypotension and in terms of possible decline in renal function.[1-5]

Keywords

Heart Failure; Review; Pharmacology; Practical View

Mailing Address: José Albuquerque de Figueiredo Neto •
Avenida dos Holandeses, 2, Ed. Iate Classic, apt.1202. Ponta D'areia, CEP 65077-357, São Luís, MA – Brazil
E-mail: jafneto@terra.com.br
Manuscript received January 21, 2022, revised manuscript February 01, 2022, accepted February 16, 2022

DOI: https://doi.org/10.36660/abchf.20220002

Adverse effects

The principal effects to be considered are hyperkalemia, allergies, coughing, and angioedema. The last two of these are related to increased bradykinins and other prostaglandins. These drugs are contraindicated in pregnant women because of the possibility of inducing kidney damage in the fetus and should therefore also be avoided in women of fertile age.[3]

Angiotensin ii receptor blockers (ARBs)

Mechanism of action

Based on what was described above in relation to the role played by angiotensin II in cardiac remodeling, ARBs act to block this effect at the level of the AT1 receptor, in contrast to the ACEIs which act on production of this peptide. In this case, conversion of angiotensin I into angiotensin II follows its normal cycle, i.e., there is an elevated serum angiotensin II level, but its AT1 receptors will be blocked.[1] It should be remembered that there is also an AT2 receptor that is not blocked by the ARBs, which is one of the features that lead to a degree of preference for the ACEIs over this group. Bearing in mind that ACE acts normally in patients who are taking these drugs, inactivation of bradykinin and other vasodilator peptides continues as normal, meaning that this group has lower vasodilatory power and fewer related side-effects.[2]

Pharmacokinetics

This class also has presentations in the form of drug or pro-drug, which are absorbed and activated in the gastrointestinal tract and cleared renally and can precipitate deterioration of creatinine clearance.[2] Losartan, a member of this group, has an active metabolite with a half-life in the range of 3 to 4h,[2] with an initial dose of 50mg per day, targeting a daily maximum dose of 150mg.[3]

Adverse effects

Adverse effects are similar to those of the ACEIs, with the exception of coughing and angioedema since, as described above, they do not affect bradykinin metabolism.[6]

Practical Aspects (of use of ACEIs and ARBs):[3]

• Intolerance of ACEIs is defined as presence of persistent and debilitating coughing (which occurs in approximately 10 to 20% of cases) or occurrence of angioedema (a rare finding: < 1%). Use of ARBs is an alternative option in these cases. Rates

of other adverse effects, such as hypotension, hyperkalemia, or renal dysfunction, are similar for ACEIs and ARBs. In cases of persistent and recurrent hyperkalemia and/or loss of renal function with ACEIs/ARBs, an alternative vasodilator therapy should be considered (in general, a combination of nitrate and hydralazine).

• Due to the risk of deterioration of renal function, hyperkalemia, and arterial hypotension, ACEIs/ARBs should be introduced at low doses (especially in patients with borderline blood pressure) and titrated progressively, until the target dose is attained, guaranteeing the benefits documented in large multicenter clinical trials.

• An increase of up to 50% over baseline creatinine, or an absolute value of up to 3 mg/dL, or an estimated creatinine clearance > 25 mL/min/m^2 is acceptable without requiring that drug dosages be reduced (ACEI or ARB). In these cases, it is recommended to maintain strict surveillance of renal function and potassium levels. If potassium exceeds 5.5 mEq/L, or creatinine exceeds 3.5 mg/dL, or clearance is below < 20 mL/min/m^2, then withdrawal of the ACEI or ARB should be considered .

• Combinations with ACEI and ARB should not be administered to patients taking aldosterone antagonists because of the risk of side effects, especially hyperkalemia.

Angiotensin receptor-neprilysin inhibitor (ARNI - Sacubitril/ Valsartan):

Mechanism of action

Still with regard to the pathophysiology of Heart Failure, we need to focus on the effects of the natriuretic peptides – brain, atrial, and type C – which are endogenous hormones capable of stimulating natriuresis, vasodilation, and diuresis. Brain and atrial natriuretic peptides have the greatest effects on the many different factors that determine heart failure and are released when ventricular and atrial muscles, respectively, are distended. In addition to the effects described above, they can also reduce the effects of angiotensin II, contributing to block the renin-angiotensin-aldosterone system. These peptides have short half-lives and are metabolized at the renal, hepatic, and pulmonary levels by neutral endopeptidase or neprilysin.[4,5] Use of these drugs alone had no impact on morbidity or mortality rates of patients with HF, but, according to the PARADIGM – HF study, the combination of sacubitril (oral neprilysin inhibitor) with valsartan (angiotensin receptor blocker) achieved greater reductions in hospital admissions and improvements in quality of life and mortality among patients with HF than ACEI, previously considered the first line of treatment.[7,8]

Pharmacokinetics

Sacubitril is a pro-drug metabolized at the hepatic level and excreted via the kidneys, in common with valsartan, so it should also be avoided in patients with impaired creatinine clearance.[5] Treatment with this drug should be optimized by degrees, observing which drugs the patient had been taking previously (ACEI or ARB) to minimize side effects and interactions with them. The initial dose is 24/26mg[3] or 49/51mg[6] twice a day, depending on the reference followed, progressing to a maximum dose of 97/103mg twice a day.

Adverse effects

Beyond the adverse effects of valsartan (and of ARBs in general) already known, there is also a possibility of hypersensitivity to sacubitril and patients with borderline blood pressure tend to have more episodes of hypotension when taking sacubitril/valsartan. It should be noted that for patients who have been taking an ACEI, a 36h period without medications should be allowed to elapse before starting them on sacubitril/valsartan, because of a risk of angioedema. Patients on an ARB do not need to undergo this pause in treatment.[4,5]

Practical aspects

• Test renal function and electrolytes.9

• Drug tolerability, side effects, and monitoring with laboratory tests are similar with ARNI to with ACEIs or ARBs, already mentioned above.[9]

• Serum levels of urea, creatinine, and potassium should be monitored 1 to 2 weeks after starting treatment and after titrations.[9]

• If the patient had been taking ACEI and it is decided to change to ARNI, it is necessary to allow 36h to elapse without taking an ACEI before starting on sacubitril/valsartan. This washout period is to reduce the risk of angioedema and no washout is needed to change from an ARB to an ARNI.[10]

Beta blockers

Beta-blockers (BB) are first-line drugs for treatment of heart failure with reduced ejection fraction (HFrEF), because they yield clinical benefits observed in overall mortality, death from HF, and sudden death, in addition to improving symptoms and reducing rates of hospital readmissions for HF.[11-14] Of the options available, those that have demonstrated consistent results are Bisoprolol,[11] Metoprolol Succinate,[12] Carvedilol.[13] Additionally, Nebivolol was tested in patients with HF over the age of 70 years and reduced the primary clinical outcome (total mortality and cardiovascular hospital admissions), but did not have a statistically significant impact on total mortality in isolation.[15] (Chart 1)

Reverse remodeling, increased left ventricle ejection fraction (LVEF), and the consequent improvement in HF symptoms occur just a few weeks or months after introduction of the BB. It is important to start treatment with low doses, with progressive increases every 2 weeks, depending on tolerability (monitoring bradycardia and worsening of HF symptoms). If symptoms are accentuated, adjustments of diuretics and vasodilators should be attempted before reducing dosage or suspending the BB. BB are also indicated for patients with asymptomatic left ventricle (LV) dysfunction and for control of ventricular frequency in patients with HFrEF and chronic atrial fibrillation (AF).[3,16]

Chart 1 – Recommendations from the Brazilian Heart Failure Guidelines – 2018.[3]

Bisoprolol, carvedilol, and metoprolol succinate for symptomatic LV dysfunction to reduce morbidity and mortality. Class/Evidence Level (EL): I/A
Nebivolol for symptomatic LV dysfunction in patients > 70 years of age. Class/EL: IIB/B

LV: left ventricle.

Mechanism of action and pharmacokinetics

Since the catecholamines exert positive chronotropic and inotropic actions, antagonists of their receptors do the opposite, reducing heart rate and myocardial contractility. When tonic stimulation of the receptors is low, this effect is correspondingly modest. However, when the sympathetic nervous system is activated, such as during exercise or stress, the receptor antagonists attenuate the expected increase in heart rate.[2]

All of the clinically available BB are competitive antagonists. Non-selective Beta-blockers block the β1 and β2 receptors, whereas cardioselective types have a predilection for β1. Some selective β1 antagonist drugs with clinical applications in HF are: Metoprolol, Bisoprolol and Nebivolol. They have oral presentations and good bioavailability; Metoprolol and Bisoporolol have half-lives from 3 to 4 hours, while Nebivolol has a half life of 10 to 30 hours.[2,17]

These drugs antagonize β1 receptors at doses 50 to 100 times lower than those needed to block β2 receptors. This cardioselectivity is significant at low doses but is lost at elevated doses. [2,17] Consequently, patients with HF and some degree of lung disease, including asthmatics, can take BBs, but those with greater β1 selectivity (such as bisoprolol and nebivolol) are preferred.[3,7]

With regard to Carvedilol, this is a non-selective BB that antagonizes β1 receptors and also α1 receptors, blockage of which produces peripheral vasodilation, reducing arterial blood pressure. This drug is also well-tolerated via oral route and its plasma half-life is from 7 to 10 hours.[2,13]

Adverse effects

In the cardiovascular system, bradycardia is the normal response to β blockade, but β antagonists may cause bradyarrhythmia in patients with partial or complete atrioventricular conduction defects. Particular caution should be exercised with patients who are being treated with other drugs, such as verapamil or antiarrhythmics, which can impede sinoatrial node function and adequate atrial-ventricular conduction.[7] In cases of atrioventricular blockade, other drugs that act on the atrioventricular node, such as digoxin and amiodarone, should be withdrawn first.[3]

The most important adverse effect on pulmonary function is caused by β2 receptor blockade, in the bronchial smooth muscle. This can be particularly dangerous in patients with bronchospastic disease.[2]

Practical Aspects

• The beneficial results of BBs may only become apparent after several months of use and in some patients they occur later still (after 12 months).[3]

• Some patients may report discrete functional deterioration at the start of treatment with BBs, but should be encouraged to continue using the medication.[3]

• The majority of patients with HFrEF, particularly those at less advanced functional classes, can be treated with BBs by physicians who are not specialists in HF.[3]

• Patients at more advanced functional classes should be reassessed with more frequent visits when started on BBs and may benefit from assessment by a specialist in HF.[3]

• Patients with lung disease – and even asthmatics – can be treated with BBs, giving preference to those with greater selectivity β1 (such as bisoprolol and nebivolol).[3,7]

• If atrioventricular blockade occurs, the first response should be to reduce or withdraw other drugs that act on the atrioventricular node, such as digoxin and amiodarone.[3]

• Transitory fluid retention may occur at initiation of beta blockers or on uptitration, which may require reevaluation of diuretic dosages.[3]

Mineralocorticoid receptor antagonists

The biological effects of aldosterone have significant repercussions for the pathophysiology of Heart Failure, making it extremely important to reduce this mineralocorticoid as part of treatment for the condition.[18]

In HF, these medications are indicated for symptomatic LV dysfunction, at New York Heart Association (NYHA) functional classes II to IV, combined with standard treatment with ACEI or ARB and BB,[3] with a maximum evidence level (I-A).

Eplerenone has a more selective action, but is not available on the Brazilian market, although its results can be extrapolated to sprinolactone.[19]

Mechanism of action and Pharmacokinetics

When aldosterone binds to Mineralocorticoid Receptors (MR) located in the final portion of the distal tubule and in the collecting duct, it induces synthesis of Aldosterone Induced Proteins (AIP), which has the biological consequences of inducing retention of sodium and water, in addition to excretion of K^+ and H^+.[2]

Mineralocorticoid receptor antagonists (MRAs - spironolactone and eplerenone) competitively inhibit binding of aldosterone to MR and are not capable of inducing formation of AIP, thereby blocking the effect of aldosterone in the body, which improves endothelial function and nitric oxide bioavailability, with possible antisclerotic effects, in addition to reduction of myocardial fibrosis having been demonstrated.[20]

Adverse effects

Since these are diuretic and potassium-sparing drugs, they may have side effects such as hypotension, dehydration, and hyponatremia, in addition to hyperkalemia, so it is necessary to monitor potassium levels and regularly test renal function.[19] MRAs should therefore be avoided in patients with > 2.5 mg/dL or hyperkalemia. Additionally, sprinolactone also has an antiandrogenic effect and inhibits steroidogenesis, which can cause gynecomastia and loss of libido,[20] which are not as common with eplerenone, because it is more selective.

Practical aspects

• Check renal function and electrolytes (especially K^+), particularly after initiating treatment/increasing dosage.[9]

• Consider titration of dosage after 4 to 8 weeks.

• If K^+ > 5.5 mmol/L or Creatinine >2.5 mg/dL and glomerular filtration rate (GFR) < 30 mL/min/1.73 m^2, halve the dosage and monitor blood tests.[9]

• If K^+ > 6.0 mmol/L or Creatinine >3.5 mg/dL and GFR <20 mL/min/1.73 m^2, withdraw MRAS immediately and consult a specialist.[9]

SGLT2 inhibitors

Recently, major advances have been achieved in relation to antidiabetic medications and cardiovascular risk. This has yielded a new approach to treatment of HFrEF, different from conventional blockage of the system – the sodium-glucose cotransporter 2 inhibitors (SGLT2i).[1] These drugs initially demonstrated their cardiovascular safety in patients with type 2 Diabetes Mellitus (DM2), with beneficial effects, such as reduction of cardiovascular events, cardiovascular mortality, and hospital admissions for HF, using empagliflozin.[2] Later, other studies revealed benefits of this class, extending to Canaglifozin,[3] Dapaglifozin and Empagliflozin, including in patients without diabetes[4,5] and, finally, to Sotagliflozin (not available in Brazil).[6] (Chart 2)

Mechanism of action and Pharmacokinetics

The mechanisms underlying cardiovascular protection and the renal effects of SGLT2 inhibitors in patients with and without DM2 are still not entirely understood, although several mechanisms have been proposed.[20] These new drugs act to inhibit glucose reabsorption in the renal tubules, by inhibiting the SGLT2 receptors in the distal convoluted tubule (DCT), provoking glycosuria. Reduction of glycemia is also related to natriuresis, osmotic diuresis, modest weight loss, increased hematocrit, and reduction of arterial blood pressure. The hemodynamic effects occur early, since as endothelial function and vasodilation improve, there are also reductions in preload and afterload and also in cardiac fibrosis.[21]

These drugs have shown a high affinity for SGLT2, low affinity for SGLT1 (which guarantees better tolerability), good oral route bioavailability, and prolonged life, permitting administration of an oral dose once a day. Additionally, metabolism does not involve active metabolites, so they also have a limited drug interaction profile. Finally, no clinically relevant changes in the pharmacokinetics of these drugs have been observed in patients with DM2, kidney failure, or mild/moderate liver failure.[22]

Adverse effects

In general, SGLT2 inhibitors have a good tolerability profile and are not associated with many adverse effects, beyond a small chance of developing hypoglycemia, despite the glycosuria.[10] The glycosuria increases the risk of infections of the genitourinary tract, especially genital infections (a 4% increase compared to placebo), and infections of the urinary tract (a 1% increase in relation to placebo).[22] However, it is valid to point out that, in general, these are not severe infections and can be easily managed with antibiotic therapy alone.[22-24] Finally, some concerning observations that need to be confirmed in clinical trials and must be investigated more intensely involve a potentially worrying trend for an increased incidence of breast and bladder cancer – clearly this must be investigated more intensely in clinical trials.[22,25]

Practical Aspects

• Test renal function when starting treatment and monitor it regularly. It is known that GFR reduces slightly after starting treatment, but SGLT2i appear to offer kidney protection.[9]

• Monitor glycemia regularly, primarily when the patient is diabetic. Consider modifying other diabetic drugs.[9]

Chart 2 – Recommendations from the Brazilian Heart Failure Guidelines – 2021, for use of SGLT2 inhibitors in treatment of HFrEF.[3]

Dapaglifozin or Empagliflozin are indicated in patients with symptomatic HFrEF, diabetic or not, with maximum optimized dose of BB, aldosterone antagonist, ACEI/ARB, or ARNI, to reduce cardiovascular outcomes and progression of renal dysfunction. Class/Evidence level (EL): I/A
Canaglifozin, Dapaglifozin, or Empagliflozin for prevention of hospital admissions for HF in patients with DM2 who have cardiovascular risk factors for atherosclerosis or established atherosclerotic cardiovascular disease. Class/EL: I/A
Dapaglifozin or Empagliflozin as initial antidiabetic medication, combined or not with metformin in patients with HFrEF. Class/EL: I/A
Dapaglifozin or Empagliflozin in patients with HFrEF for prevention of reduction of renal function in patients with and without diabetes, with TGF > 20 Ml/min/1.73 m^2. Class/EL: IIa/A

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor-neprilysin inhibitor; BB: beta-blockers; DM2: type 2 diabetes mellitus; GFR: glomerular filtration rate; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; SGLT2i: sodium-glucose cotransporter 2 inhibitors.

Nitrates and Hydralazine

Mechanism of action

The combination of hydralazine and nitrates has arterial and venous vasodilatory effects. This combination is able to reduce preload and afterload, reduce atrial and left ventricular wall tension, improve LV ejection fraction, and induce reverse remodeling, having demonstrated favorable effects on left ventricular function and HF-associated mortality.[26] Additionally, the combination maintains a balance between nitric oxide and reactive oxygen species (ROS), which is important for maintenance of cardiovascular health.[3] The V-HeFT I study[27] confirmed these beneficial effects, with reduction in mortality compared with placebo, but the combination did not surpass the benefit of ACEIs, as was later demonstrated in the V-HeFT II study.[28]

However, according to the A-HeFT (African-American Heart Failure Trial) study, hydralazine and nitrate demonstrated considerable additional benefits in self-declared black patients, at NYHA functional class III-IV who were already on standard treatment, with a 33% reduction in hospital admissions and 43% drop in total mortality.[29]

Pharmacokinetics

In the A-HeFT study, the initial dose, available as a fixed dose, was 37.5 mg of hydralazine and 20 mg of isosorbide dinitrate, oral route, 3 times/day, with a maximum dose of 75 mg and 40 mg, 3 times/day, depending on tolerance and side effects. In Brazil, there is no fixed dose available and the initial dose suggested is 25 mg hydralazine and 10 mg of nitrate, 3 times a day, increasing progressively up to 100 mg per day of hydralazine and 40 mg per day of nitrate, also 3 times a day, or up to the maximum dose tolerated.[20]

Side effects

The most common side effects of nitrate are related to vasodilation: orthostatic hypotension, tachycardia, and pulsating headaches. The most frequent side effects of hydralazine are headaches, nausea, anorexia, palpitations, diaphoresis, and rubor, and when given in higher doses there is a small chance of development of a syndrome similar to lupus erythematosus.[1]

Practical Aspects

• Introduction of vasodilators may be indicated for patients who exhibit deterioration of renal function and/or hyperkalemia when taking ACEI/ARBs, for those who do not improve when put on optimized drug therapy, or in whom there is documented persistence of signs of elevated peripheral resistance.[3]

• Nitrates alone may be useful to relieve orthopnea, paroxysmal nocturnal dyspnea, effort dyspnea, or angina, but continuous use is associated with development of tolerance.[10]

Ivabradine

In 1987, the Framingham Study showed that heart rate (HR) was associated with all causes of cardiovascular and coronary mortality over 30 years of follow-up.[30] A review of the literature indicated that elevated HR is associated with worse prognosis in HF and can be considered a treatment target.[31]

Mechanism of action

As such, Ivabradine can be considered part of the therapeutic arsenal for HF, since it provokes negative chronotropism by inhibiting sinoatrial node pacemaker activity through selectively blocking If current. However, it does not affect myocardial contractility, ventricular repolarization, or intracardiac conduction.[1]

The SHIFT study showed that when ivabradine was added in patients with sinus rhythm, with HR ≥ 70 bpm, and LVEF ≤ 35%, who remained symptomatic despite normal drug treatment, it was associated with a reduction in the composite outcome of cardiovascular death or hospital admission for HF, but not with cardiovascular mortality or all causes mortality.[32]

Pharmacokinetics

The initial dose recommended is 5 mg twice a day. In patients with regard to whom there are concerns that a reduction in HR could cause hemodynamic compromise or who have conduction defects, the initial dose can be 2.5 mg twice a day. The dose should be adjusted every 2 weeks with the objective of achieving an HR of 50-60 bpm up to a maximum dose of 7.5 mg twice a day.[33]

Renal failure has a minimal impact on the pharmacokinetics of ivabradine, because it is primarily metabolized by cytochrome p450 (CYP3A4) in the liver and in the gastrointestinal tract.[34,35] Plasma concentration peaks after approximately 1 h in fasting patients and food intake can delay this peak by 1 h. It has been demonstrated that mild liver failure can increase ivabradine levels by up to 20%[36] and the drug is contraindicated in severe liver failure.[32]

Adverse effects

The side effects of ivabradine most commonly reported in clinical practice are bradycardia, AF, and phosphenes.[37] In the SHIFT study, 5% of the patients exhibited symptomatic bradycardia and the drug was associated with a small increase in the incidence of AF. Its use should therefore be reconsidered in patients who have paroxysmal AF.[32] Although it is not considered that ivabradine prolongs the QT interval, it has been associated with torsade de pointes in experimental models and in combination with other medications[38-41] and caution should be exercised when it is used in conjunction with medications that prolong the QT interval. Ivabradine should not be taken during pregnancy.

Practical aspects:[9]

• Monitor heart rate, arterial blood pressure, and clinical status.

• Start with an initial dose of 5 mg 2x/day.

• The daily dose can be increased, reduced, or withdrawn depending on the patient's heart rate at rest. If resting heart rate is between 50 and 60 beats per minute, the current dose should be maintained.

• Titrate doses every 2 weeks, if possible, aiming for the target dose or the highest dose tolerated, on the basis of heart rate at rest.

• Treatment should be reduced or withdrawn if heart rate at rest remains persistently below 50 b.p.m. or if there are symptoms of bradycardia:

• Ivabradine should be withdrawn if a patient develops persistent/continuous AF during treatment with it.

• The visual phenomena are generally transitory and disappear during the first months of treatment with ivabradine and are not associated with severe retina dysfunction. However, withdrawal of ivabradine should be considered if they cause the patient discomfort.

• If symptoms occur in patients with intolerance to lactose or galactose (a component of the ivabradine tablet), it may be necessary to withdraw the medication.

Digoxin

The DIG study randomized 6800 patients with HFrEF to receive digoxin or placebo and showed that the drug did not reduce mortality, but did reduce hospital admissions for HF.[41] Consequently, the guidelines recommend that digoxin be considered an adjunct to optimized therapy in symptomatic patients with HFrEF. If the patient has sinus rhythm, ivabradine should be preferred, but if there is AF, digoxin can be used alone,[3,33] although there is considerable controversy about the safety of using digoxin in patients with AF.[43]

Mechanism of action

Digoxin is a cardiac glycoside that belongs to the drug class digitalis glycosides. It has two mechanisms of action. Inhibition of the Na-K ATPase pump induces increased intracellular sodium, followed by a relative reduction in expulsion of calcium from the sarcomere, causing an increase in cardiac contractility. The other mechanism encompasses inhibition of the atrioventricular node (AVN). Elevation of the calcium levels leads to prolongation of phases 4 and 0 of the cardiac action potential, thereby increasing the refractory period of the AVN. The drug also stimulates the parasympathetic nervous system, reducing electrical conduction in the AVN and heart rate.[1,44]

Pharmacokinetics

All of the cardiac glycosides are widely distributed through the tissues, including in the central nervous system (CNS). Almost two thirds of digoxin is excreted unaltered by the kidneys. Its renal clearance is proportional to creatinine clearance, with a half-life of 36 to 40 hours in patients with normal renal function.[1,44] It is necessary to adjust the dose in the presence of renal function deficiency (Table 1). Corticosteroids and diuretics that cause potassium depletion increase the toxicity of digoxin.[45,46]

Adverse effects

Digoxin toxicity is clinically relevant, because it can lead to fatal cardiac arrhythmias.[47] One clinical trial has suggested that serum levels exceeding 1.2 ng/mL are associated with increased risk of death in patients with AF.[48] However, toxicity can occur at lower levels in the presence of other risk factors, such as low body weight, advanced age, reduced renal function, and hypokalemia.[49,50]

The incidence of side effects is estimated at up to 20%, around 50% of which are cardiac symptoms (such as arrhythmia and 1st degree AV block), 25% are gastrointestinal tract symptoms (anorexia, nausea, vomiting), and the remainder are CNS manifestations (headache, malaise, fatigue, disorientation) and other side effects. Digoxin is contraindicated in the following conditions: acute myocardial infarction, hypersensitivity to the drug, ventricular fibrillation, myocarditis, hypomagnesemia, hypokalemia, and Wolf-Parkinson-White syndrome.[50] Use of digoxin in pregnancy appears to be safe.[3]

Practical Aspects:[10]

• In patients taking Digoxin, serum potassium and creatinine should be measured whenever the digoxin dose is increased or drugs that could cause interactions are introduced, since there is a risk of toxicity with digoxin.

• Patients with impaired renal function, the elderly, those with low body weight, and women are at increased risk of digoxin toxicity and need more frequent monitoring.

• Routine digoxin level tests are unnecessary to assess toxicity and should not be used to guide long-term treatment.

Diuretics in heart failure

The majority of patients with Heart Failure with reduced Ejection Fraction (HFrEF) need a diuretic to control symptoms of congestion, particularly if they are acutely decompensated.[51] (Chart 3) Loop diuretics (especially furosemide) are the preferred agents, although use of thiazide in patients with little response to increasing loop diuretic doses has been recommended in observational studies or small scale trials.[52] The main adverse effects of diuretics are volume and/or electrolyte depletion and excessive diuresis can also predispose to hypotension and acute kidney damage. Some patients can benefit from a diuretic dosing regimen, by which they weigh themselves daily and dosage is adjusted if weight increases or reduces beyond a specific range.[7]

However, it is important to emphasize that these diuretics are symptomatic drugs, since no randomized clinical trials have demonstrated increased survival associated with their use in ambulatory patients with chronic HF.[3] Additionally, observational studies have demonstrated potential harmful effects on the RAAS of chronic and continual use of diuretics,[54,55] suggesting association with worse clinical outcomes. It is therefore recommended to always use the smallest therapeutic dose necessary with continual use of diuretics.[53] (Table 2)

Loop diuretics

Compared with all of the other classes of diuretics, these drugs exhibit the greatest efficacy for mobilization of Na^+ and Cl^- in the body. They produce abundant quantities of urine, because they act on the thick ascending limb of Henle's loop, where the greatest resorption rate occurs, in comparison with other parts of the nephron. Furosemide is the most used drug in this group.[2,17] Ethacrynic acid has a steeper dose-response curve than Furosemide, but is associated with more adverse effects than observed with other loop diuretics and so its use is limited. Bumetanide is much more potent than furosemide.

Table 1 – Recommended Dosage

Recommended dose of digoxin according to GFR (ml/min/1.73m²)	
GFR ml/min/1.73m²	**Dose mg/dia**
>90	0.25
60 - 90	0.125
30 - 60	0.125 em dias alternados
<30	Do not use

Source: adapted from DiDomenico et al.[51]

Chart 3 – Recommendations from the Brazilian Heart Failure Guidelines – 2018[3]

Loop diuretics to control congestion. Class/Evidence level (EL): I/C
Thiazide diuretic combined with a loop diuretic to control persistent congestion, despite optimized treatment and increased loop diuretic dosages. Class/EL: I/B [53]
Initiate diuretics while HFrEF asymptomatic. Class/EL: III/C

HFrEF: heart failure with reduced ejection fraction.

Table 2 – Diuretics most frequently used in decompensated HF. Source: Heart Failure Guidelines Coordinating Committee, 2018

Medication	Route	Interval	Minimum dose	Maximum dose
Loop diuretic				
Furosemide	IV/PO	4/4h-6/6h Variable	20 mg 40 mg	240 mg 240mg
Bumetanide	IV	6/6h	0.5-2mg	10 mg
Thiazide				
Hydrochlorothiazide	PO	12/12h-24/24h	25 mg	100 mg
Chlorthalidone	PO	12/12h-24/24h	12.5mg	50 mg
Indapamide	PO	24/24h	mg	5 mg

IV: intravenous; PO: by mouth.

Mechanism of action

These drugs inhibit activity of the Na^+-K^+-$2Cl^-$ cotransporter in the thick ascending limb of Henle's loop, which is why they are called loop diuretics. This is the most effective mechanism for provoking diuresis and is responsible for resorption of 25 to 30% of filtered NaCl. For example, although the DCT reabsorbs around 65% of filtered Na^+, the diuretics that only act on this tubule have limited efficacy because the thick ascending limb reabsorbs a large proportion of the rejected material. Additionally, those that predominantly act on sites after the thick ascending limb (such as the Convoluted Distal Tubule and the Collector Tubule) have limited efficacy, because only a small percentage of the filtered Na^+ reaches these more distal sites.[2,17]

Pharmacokinetics

Approximately 65% of Furosemide is excreted unaltered in urine and the remainder is conjugated with glucuronic acid in the kidneys. Thus, the half-life of furosemide clearance is prolonged in patients with kidney disease who are free from liver disease. In contrast, bumetanide and torsemide exhibit significant hepatic metabolism, so that their half-lives can be extended in the presence of liver disease.[2,17,56] (Table 3)

The mean oral availability of furosemide is approximately 60% and the natriuretic response is rapid, with peak activity at 20 to 30 minutes and duration of 4 to 6 hours.[57] Torsemide and Bumetadine have similar half-life and duration relatively, but they are more powerful and have greater bioavailability (from 60 to 80%).[58]

As a class, loop diuretics have short clearance half-lives and are not available in slow-release preparations. As a result, intervals between administration must be short to maintain them at adequate concentrations within the tubule lumen.[7]

Adverse effects

Loop diuretics act rapidly and provoke changes in the composition of urine and increase the volume excreted. In

relation to electrolytes, these drugs considerably deplete Na^+, Ca^{+2}, and K^+ and can also deplete Mg^{+2}, especially in the elderly. Particularly in the case of hyponatremia, the consequence of less Na^+ arriving at the DCT and collector tubule can, in the final analysis, trigger hypochloremic and hypokalemic metabolic alkalosis.[57]

Additionally, another classic adverse effect associated with this class of drugs is ototoxicity (in general reversible). This emerges as a buzzing, compromising hearing, with deafness, vertigo/dizziness, and feelings of blocked ears. It is commonly more related to cases of intravenous administration of this drug class or in cases of combinations with other medications capable of provoking this, such as aminoglycosides.[2,17]

It is worth noting that loop diuretics can also interfere in homeostasis of other metabolites. For example, uric acid (with hyperuricemia, and in some cases it can provoke gout), glucose (with hyperglycemia), and cholesterol (with increased plasma levels, especially of LDL).[2,56]

People with hypersensitivity to sulfonamides have a contraindication to taking loop diuretics derived from them. Additionally, some medications can interfere with their efficacy, such as the non-steroidal anti-inflammatory drugs (NSAIDs).[2]

Thiazide

Mechanism of action

Thiazide derivatives increase diuresis, primarily acting on the DCT, reducing resorption of Na^+ by inhibition of the Na^+/Cl^- cotransporter in the luminal membrane of tubules.[2,17,56]

This increase in urinary output also causes increased urinary excretion of some other elements, including K^+ and Mg^{+2}, especially in the elderly. The cause of hypokalemia is the fact that inhibitors of the Na+/Cl- cotransporter provoke a filtrate with higher Na^+ concentration and consequently increase urinary excretion of K^+ because of the exchange mechanism that occurs in the collector tubule (discussed in the section on mineralocorticoid antagonists). In turn, hypomagnesemia is an effect that is particularly seen in the elderly because administration of these drugs can cause magnesiuria, through a little-understood mechanism.[17]

In relation to electrolytes that are spared, excretion of Ca^{+2} is reduced because chronic administration of thiazide provokes volume depletion, which requires more intense proximal resorption, but also because the class has the effect of increasing resorption of this cation in the DCT.

Pharmacokinetics

It is important to emphasize that the pharmacokinetics of thiazide diuretics can be very variable, depending on the drug in question (Table 4), but in general, the maximum excretion of Na^+ load is just 5%, because around 90% of the Na^+ load filtered is reabsorbed before reaching the DCT. Hydrochlorothiazide is one of the main members of this class, with intestinal absorption of 65%, plasmatic protein binding of 40%, and clearance half-life of approximately 10 hours, with 95% of the dose eliminated unaltered via urine. The duration of hydrochlorothiazide activity is 18-24 hours. Intestinal absorption of this drug may be reduced in patients with heart failure. The natriuretic action of thiazide reduces rapidly when glomerular filtration is less than 30 ml/minute and these

Table 3 – Na+-K+-2Cl- cotransporter inhibitors (loop diuretics)

Drug	Relative Potency	Oral availability	Half-life (hours)	Excretion pathway
Furosemide	1	~60%	~1.5h	~65%R ~35%M[a]
Bumetanide	40	~80%	~0.8h	~62%R ~38%M

[a] For furosemide, metabolism is primarily in the kidneys. R: renal excretion of the intact drug; M: metabolism.

Table 4 – Na+/Cl- cotransporter inhibitors (thiazide and similar)

Drug	Relative Potency	Oral availability	Half-life (hours)	Excretion pathway
Hydrochlorothiazide	1	~70%	~2.5h	R
Chlorthalidone	1	~65%	~47h	~65%R ~10%B ~25%U
Indapamide	20	~93%	~14h	M

R: renal excretion of the intact drug; M: metabolism; B: excretion of the intact drug in the bile; U: excretion pathway unknown.

drugs become ineffective when glomerular filtration is less than 10ml/minute.[2,17,58]

Adverse effects

The most severe adverse effects of thiazides are related to abnormalities of fluid and electrolyte balance. These adverse effects include depletion of extracellular volume, hypotension, hypokalemia, hyponatremia, hypochloremia, metabolic alkalosis, and hypomagnesemia.[56] These diuretics have also shown the potential to interfere in metabolism of other compounds, explaining the emergence of hyperuricemia, hyperglycemia, and hyperlipemia.[2,17]

Hypokalemia may be related to reduction in insulin secretion, which would explain the changes to glucose metabolism, such as increased tolerance. Control of diabetes may therefore be compromised during treatment. Additionally, thiazides can cause increases of 5 to 15% in serum cholesterol concentration and also increases in serum low density lipoproteins.[2,17]

Rarely, thiazide diuretics can provoke disorders of the central nervous system (for example: vertigo/dizziness, paresthesias, xanthopsia, and weakness) and the gastrointestinal tract (for example: anorexia, nausea, vomiting, cramps, diarrhea, constipation, cholecystitis, and pancreatitis), hematological disorders (for example: blood dyscrasia) and dermatological disorders (for example: photosensitivity and exanthemas).[2]

Thiazide diuretics are contraindicated for people hypersensitive to sulfonamides. In relation to drug interactions, they can reduce the effects of anticoagulants, uricosuric agents used to treat gout, sulfonylureas, and insulin and can increase the effects of anesthetics, diazoxide, glycosides, digitalis glycosides, lithium, loop diuretics, and vitamin D.

The effectiveness of thiazide diuretics can be reduced by NSAIDs and non-selective or selective COX-2 inhibitors. Amphotericin B and corticosteroids increase the risk of hypokalemia induced by these diuretics. A potentially lethal drug interaction occurs between thiazide diuretics and quinidine, because the QT interval prolongation caused by quinidine can lead to development of torsade de pointes (a polymorphic ventricular tachycardia).[2]

Practical aspects (loop diuretics and thiazide)

• Test renal function and electrolytes, particularly in patients on combined use of loop diuretics and thiazide.

• Start with a low dose, but adjust to an effective dose to achieve satisfactory diuresis, with reduction of body weight of 0.75 to 1.0 Kg/day.[9]

• Dose adjustment should be according to symptoms and/or signs of congestion, arterial blood pressure, and renal function, always targeting the smallest dose possible to maintain euvolemia – the patient's "dry weight". [9]

• Remember that excessive diuresis is more dangerous than edema, primarily because of the risk of hypovolemia and hypokalemia. [9]

• Monitor serum levels of Urea, Creatinine and K^+ between 1 and 2 weeks after initiation and after any increase in dosage.[9]

Author Contributions

Acquisition of data and Writing of the manuscript: Figueiredo VMS, Santos JVS, Bogéa BCA, Oliveira AG, Figueiredo Neto JA; Analysis and interpretation of the data and Critical revision of the manuscript for intellectual contente: Figueiredo Neto JA.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Katzung BG, Trevor AJ. Farmacologia básica e clínica. Porto Alegre: AMGH; 2017.
2. Brunton, Ll, Chabner BA, Knollmann BC. As Bases Farmacológicas da Terapêutica de Goodman & Gilman. 12th ed. Porto Alegre: AMGH, 2012.
3. Rohde LEP, Montera MW, Bocchi EA, Clausell NO, Albuquerque DC, Rassi S, et al. Diretriz Brasileira de Insuficiência Cardíaca Crônica e Aguda. Arq Bras Cardiol. 2018;111(3):436-539. doi: 10.5935/abc.20180190.
4. Colucci WS, Gottlieb SS, Yeon SB. Overview of the Management of Heart Failure with Reduced Ejection Fraction in Adults. [Internet]. Waltham, MA: UpToDate; 2020.
5. Meyer TE. Initial Pharmacologic Therapy of Heart Failure with Reduced Ejection Fraction in Adults. Waltham, MA: UpToDate; 2021.
6. Kostis WJ, Shetty M, Chowdhury YS, Kostis JB. ACE Inhibitor-Induced Angioedema: A Review. Curr Hypertens Rep. 2018;20(7):55. doi: 10.1007/s11906-018-0859-x.
7. Murphy SP, Ibrahim NE, Januzzi JL Jr. Heart Failure with Reduced Ejection Fraction: A Review. JAMA. 2020;324(5):488-504. doi: 10.1001/jama.2020.10262.
8. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-Neprilysin Inhibition Versus Enalapril in Heart Failure. N Engl J Med. 2014;371(11):993-1004. doi: 10.1056/NEJMoa1409077.
9. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. Corrigendum to: 2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure: Developed by the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC) With the Special Contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2021;42(48):4901. doi: 10.1093/eurheartj/ehab670.

10. Ezekowitz JA, O'Meara E, McDonald MA, Abrams H, Chan M, Ducharme A, et al. 2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure. Can J Cardiol. 2017;33(11):1342-433. doi: 10.1016/j.cjca.2017.08.022.

11. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet. 1999;353(9146):9-13.

12. Effect of Metoprolol CR/XL in Chronic Heart Failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet. 1999;353(9169):2001-7.

13. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, et al. Effect of Carvedilol on Survival in Severe Chronic Heart Failure. N Engl J Med. 2001;344(22):1651-8. doi: 10.1056/NEJM200105313442201.

14. Poole-Wilson PA, Swedberg K, Cleland JG, Di Lenarda A, Hanrath P, Komajda M, et al. Comparison of Carvedilol and Metoprolol on Clinical Outcomes in Patients with Chronic Heart Failure in the Carvedilol Or Metoprolol European Trial (COMET): Randomised Controlled Trial. Lancet. 2003;362(9377):7-13. doi: 10.1016/S0140-6736(03)13800-7.

15. Flather MD, Shibata MC, Coats AJ, Van Veldhuisen DJ, Parkhomenko A, Borbola J, et al. Randomized Trial to Determine the Effect of Nebivolol on Mortality and Cardiovascular Hospital Admission in Elderly Patients with Heart Failure (SENIORS). Eur Heart J. 2005;26(3):215-25. doi: 10.1093/eurheartj/ehi115.

16. Cadrin-Tourigny J, Shohoudi A, Roy D, Talajic M, Tadros R, Mondésert B, et al. Decreased Mortality With Beta-Blockers in Patients With Heart Failure and Coexisting Atrial Fibrillation: An AF-CHF Substudy. JACC Heart Fail. 2017;5(2):99-106. doi: 10.1016/j.jchf.2016.10.015.

17. Whalen K, Finkel R, Panavelil TA. Farmacologia Ilustrada. 6. ed. Porto Alegre: Artmed, 2016.

18. Dzau VJ, Colucci WS, Hollenberg NK, Williams GH. Relation of the Renin-Angiotensin-Aldosterone System to Clinical State in Congestive Heart Failure. Circulation. 1981;63(3):645-51. doi: 10.1161/01.cir.63.3.645.

19. Jaisser F, Farman N. Emerging Roles of the Mineralocorticoid Receptor in Pathology: Toward New Paradigms in Clinical Pharmacology. Pharmacol Rev. 2016;68(1):49-75. doi: 10.1124/pr.115.011106.

20. Figueiredo Neto JA. Insuficiência Cardíaca DEIC – SBC. 1. ed. Santana de Parnaíba: Manole, 2022.

21. Leeuw AE, de Boer RA. Sodium-Glucose Cotransporter 2 Inhibition: Cardioprotection by Treating Diabetes-A Translational Viewpoint Explaining its Potential Salutary Effects. Eur Heart J Cardiovasc Pharmacother. 2016;2(4):244-55. doi: 10.1093/ehjcvp/pvw009.

22. Scheen AJ. Evaluating SGLT2 Inhibitors for Type 2 Diabetes: Pharmacokinetic and Toxicological Considerations. Expert Opin Drug Metab Toxicol. 2014;10(5):647-63. doi: 10.1517/17425255.2014.873788.

23. Taylor SR, Harris KB. The Clinical Efficacy and Safety of Sodium Glucose Cotransporter-2 Inhibitors in Adults with Type 2 Diabetes Mellitus. Pharmacotherapy. 2013;33(9):984-99. doi: 10.1002/phar.1303.

24. Bailey CJ. Renal Glucose Reabsorption Inhibitors to Treat Diabetes. Trends Pharmacol Sci. 2011;32(2):63-71. doi: 10.1016/j.tips.2010.11.011.

25. Ferrannini E, Solini A. SGLT2 Inhibition in Diabetes Mellitus: Rationale and Clinical Prospects. Nat Rev Endocrinol. 2012;8(8):495-502. doi: 10.1038/nrendo.2011.243.

26. Nyolczas N, Dékány M, Muk B, Szabó B. Combination of Hydralazine and Isosorbide-Dinitrate in the Treatment of Patients with Heart Failure with Reduced Ejection Fraction. Adv Exp Med Biol. 2018;1067:31-45. doi: 10.1007/5584_2017_112.

27. Cohn JN, Archibald DG, Ziesche S, Franciosa JA, Harston WE, Tristani FE, et al. Effect of Vasodilator Therapy on Mortality in Chronic Congestive Heart Failure. Results of a Veterans Administration Cooperative Study. N Engl J Med. 1986;314(24):1547-52. doi: 10.1056/NEJM198606123142404.

28. Cohn JN, Johnson G, Ziesche S, Cobb F, Francis G, Tristani F, et al. A Comparison of Enalapril with Hydralazine-Isosorbide Dinitrate in the Treatment of Chronic Congestive Heart Failure. N Engl J Med. 1991;325(5):303-10. doi: 10.1056/NEJM199108013250502.

29. Taylor AL, Ziesche S, Yancy C, Carson P, D'Agostino R Jr, Ferdinand K, et al. Combination of Isosorbide Dinitrate and Hydralazine in Blacks with Heart Failure. N Engl J Med. 2004;351(20):2049-57. doi: 10.1056/NEJMoa042934.

30. Kannel WB, Kannel C, Paffenbarger RS Jr, Cupples LA. Heart Rate and Cardiovascular Mortality: The Framingham Study. Am Heart J. 1987;113(6):1489-94. doi: 10.1016/0002-8703(87)90666-1.

31. Oliva F, Sormani P, Contri R, Campana C, Carubelli V, Cirò A, et al. Heart Rate as a Prognostic Marker and Therapeutic Target in Acute and Chronic Heart Failure. Int J Cardiol. 2018;253:97-104. doi: 10.1016/j.ijcard.2017.09.191.

32. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, et al. Ivabradine and Outcomes in Chronic Heart Failure (SHIFT): A Randomised Placebo-Controlled Study. Lancet. 2010;376(9744):875-85. doi: 10.1016/S0140-6736(10)61198-1.

33. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. Eur Heart J. 2021;42(36):3599-726. doi: 10.1093/eurheartj/ehab368.

34. Ragueneau I, Laveille C, Jochemsen R, Resplandy G, Funck-Brentano C, Jaillon P. Pharmacokinetic-Pharmacodynamic Modeling of the Effects of Ivabradine, A Direct Sinus Node Inhibitor, On Heart Rate in Healthy Volunteers. Clin Pharmacol Ther. 1998;64(2):192-203. doi: 10.1016/S0009-9236(98)90153-9.

35. Fox K, Ford I, Ferrari R. Ivabradine in Stable Coronary Artery Disease. N Engl J Med. 2014;371(25):2435. doi: 10.1056/NEJMc1413158.

36. Bocchi EA, Salemi VMC. Ivabradine for Treatment of Heart Failure. Expert Opin Drug Saf. 2019;18(5):393-402. doi: 10.1080/14740338.2019.1612873.

37. Martin RI, Pogoryelova O, Koref MS, Bourke JP, Teare MD, Keavney BD. Atrial Fibrillation Associated with Ivabradine Treatment: Meta-Analysis of Randomised Controlled Trials. Heart. 2014;100(19):1506-10. doi: 10.1136/heartjnl-2014-305482.

38. Frommeyer G, Weller J, Ellermann C, Leitz P, Kochhäuser S, Lange PS, et al. Ivabradine Aggravates the Proarrhythmic Risk in Experimental Models of Long QT Syndrome. Cardiovasc Toxicol. 2019;19(2):129-35. doi: 10.1007/s12012-018-9482-y.

39. Hancox JC, Melgari D, Dempsey CE, Brack KE, Mitcheson J, Ng GA. hERG Potassium Channel Inhibition by Ivabradine May Contribute to QT Prolongation and Risk of Torsades de Pointes. Ther Adv Drug Saf. 2015;6(4):177-9. doi: 10.1177/2042098615595546.

40. Mittal SR. Slow Junctional Rhythm, QTc Prolongation and Transient Torsades De-Pointes Following Combined Use of Ivabradine, Diltiazem and Ranolazine. J Assoc Physicians India. 2014;62(5):426-7.

41. Cocco G, Jerie P. Torsades de Pointes Induced by the Concomitant Use of Ivabradine and Azithromycin: An Unexpected Dangerous Interaction. Cardiovasc Toxicol. 2015;15(1):104-6. doi: 10.1007/s12012-014-9274-y.

42. Digitalis Investigation Group. The Effect of Digoxin on Mortality and Morbidity in patients with heart failure. N Engl J Med. 1997;336(8):525-33. doi: 10.1056/NEJM199702203360801.

43. Sethi NJ, Nielsen EE, Safi S, Feinberg J, Gluud C, Jakobsen JC. Digoxin for Atrial Fibrillation and Atrial Flutter: A Systematic Review with Meta-Analysis and Trial Sequential Analysis of Randomised Clinical Trials. PLoS One. 2018;13(3):e0193924. doi: 10.1371/journal.pone.0193924.

44. Ren Y, Ribas HT, Heath K, Wu S, Ren J, Shriwas P, et al. Na+/K+-ATPase-Targeted Cytotoxicity of (+)-Digoxin and Several Semisynthetic Derivatives. J Nat Prod. 2020;83(3):638-48. doi: 10.1021/acs.jnatprod.9b01060.

45. Kau MM, Kan SF, Wang JR, Wang PS, Lau YT, Wang SW. Acute Effects of Digoxin on Plasma Aldosterone and Cortisol in Monkeys. Metabolism. 2009;58(1):55-61. doi: 10.1016/j.metabol.2008.08.006.

46. Wang MT, Su CY, Chan AL, Lian PW, Leu HB, Hsu YJ. Risk of Digoxin Intoxication in Heart Failure Patients Exposed to Digoxin-Diuretic Interactions: A Population-Based Study. Br J Clin Pharmacol. 2010;70(2):258-67. doi: 10.1111/j.1365-2125.2010.03687.x.

47. David MNV, Shetty M. Digoxin. In: StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK556025/.

48. Lopes RD, Rordorf R, De Ferrari GM, Leonardi S, Thomas L, Wojdyla DM, et al. Digoxin and Mortality in Patients with Atrial Fibrillation. J Am Coll Cardiol. 2018;71(10):1063-74. doi: 10.1016/j.jacc.2017.12.060.

49. Patocka J, Nepovimova E, Wu W, Kuca K. Digoxin: Pharmacology and Toxicology-A review. Environ Toxicol Pharmacol. 2020;79:103400. doi: 10.1016/j.etap.2020.103400.

50. Fu JL, Yu Q, Li MD, Hu CM, Shi G. Deleterious Cardiovascular Effect of Exosome in Digitalis-Treated Decompensated Congestive Heart Failure. J Biochem Mol Toxicol. 2020;34(5):e22462. doi: 10.1002/jbt.22462.

51. DiDomenico RJ, Bress AP, Na-Thalang K, Tsao YY, Groo VL, Deyo KL, et al. Use of a Simplified Nomogram to Individualize Digoxin Dosing versus Standard Dosing Practices in Patients with Heart Failure. Pharmacotherapy. 2014;34(11):1121-31. doi: 10.1002/phar.1480.

52. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, et al. Diuretic Strategies in Patients with Acute Decompensated Heart Failure. N Engl J Med. 2011;364(9):797-805. doi: 10.1056/NEJMoa1005419.

53. Dormans TP, Gerlag PG. Combination of High-dose Furosemide and Hydrochlorothiazide in the Treatment of Refractory Congestive Heart Failure. Eur Heart J. 1996;17(12):1867-74. doi: 10.1093/oxfordjournals.eurheartj.a014805.

54. Testani JM, Cappola TP, Brensinger CM, Shannon RP, Kimmel SE. Interaction Between Loop Diuretic-Associated Mortality and Blood Urea Nitrogen Concentration in Chronic Heart Failure. J Am Coll Cardiol. 2011;58(4):375-82. doi: 10.1016/j.jacc.2011.01.052.

55. Eshaghian S, Horwich TB, Fonarow GC. Relation of Loop Diuretic Dose to Mortality In Advanced Heart Failure. Am J Cardiol. 2006;97(12):1759-64. doi: 10.1016/j.amjcard.2005.12.072.

56. Brater DC. Pharmacology of diuretics. Am J Med Sci. 2000;319(1):38-50. doi: 10.1097/00000441-200001000-00004.

57. Trullàs JC, Morales-Rull JL, Formiga F. Tratamiento con diuréticos en la insuficiencia cardíaca aguda. Med Clin (Barc). 2014;142 (Suppl 1):36-41. doi: 10.1016/S0025-7753(14)70081-8.

58. Sinha AD, Agarwal R. Clinical Pharmacology of Antihypertensive Therapy for the Treatment of Hypertension in CKD. Clin J Am Soc Nephrol. 2019;14(5):757-64. doi: 10.2215/CJN.04330418.

Treatment of Heart Failure with reduced Ejection Fraction in 2022: The Essential Pillars

Marcely Gimenes Bonatto,[1,2] *Andressa de Oliveira Coiradas,*[1] *Lídia Ana Zytynski Moura*[3]

Serviço de Insuficiência Cardíaca e Transplante de Coração, Hospital Santa Casa de Curitiba,[1] *Curitiba, PR – Brazil*

Hospital do Rocio,[2] *Curitiba, PR – Brazil*

Pontifícia Universidade Católica do Paraná,[3] *Curitiba, PR – Brazil*

Abstract

Pharmacological treatment of heart failure with reduced ejection fraction (HFREF) has undergone changes over the years as discoveries have been made related to new systems involved in its pathophysiology and, consequently, of new therapeutic targets. For this treatment, certain drug classes have become essential and should be used in combinations with the objective of reducing the disease's high rates of morbidity and mortality. They are therefore considered the pillars of treatment for patients with HFREF.

These drug classes act on the renin-angiotensin-aldosterone system (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists), on the autonomic nervous system (beta blockers), on the natriuretic peptides system (neprilysin and angiotensin receptor inhibitors), and on the sodium-glucose cotransporter 2 (sodium-glucose cotransporter 2 inhibitors). [1]

This article will present an analytical summary of the pathophysiologic foundations and the scientific evidence that demonstrates the benefit of these medications, specifically in terms of their impact on the results of clinical trials.

Introduction

Heart failure (HF) is a complex clinical syndrome that constitutes a global health problem with ever growing prevalence. It is characterized by interactions between myocardial injury and compensatory neurohumoral mechanisms, with consequent long-term harmful effects on cardiac structure and function.[1] Despite advances in treatment approaches, 1-year hospital admission rates remain at around 31.9% and annual mortality is 7.2%.[2]

Initially, treatment of this disease was based on a hemodynamic model that attempted to increase myocardial contractility (inotropics and digitalis) and reduce preload (diuretics) and afterload (direct vasodilators). Although this model achieved symptomatic improvements for patients, it did not significantly reduce disease progression or mortality.

Years later, with the discovery of neuro-hormonal mechanisms involved in its pathophysiology, understanding of the disease changed and adoption of neuro-hormonal modulation as a therapeutic target yielded considerable improvements in morbidity and mortality. During that period, renin-angiotensin-aldosterone inhibitors (ACEI), angiotensin II receptor blockers (ARB), beta blockers (BB), and mineralocorticoid receptor antagonists (MRA) constituted what is known as "triple therapy". In 2014, with development of Sacubitril/Valsartan, an additional system was included in treatment of the disease: the natriuretic peptide system, yielding superior results to blocking the renin-angiotensin-aldosterone system (RAAS) only. Recently, a new drug class, SGLT-2 inhibitors, has demonstrated important clinical effects for treatment of the disease with reductions in morbidity, mortality, and hospitalizations when combined with standard treatment, comprising a "quadruple therapy" for treatment of HFREF (Figure 1).[1,3]

Data from the Brazilian national health system (SUS) show that there were 3,085,359 hospitalizations for HF from 2008 to 2019 – the equivalent of one third of the total number of cardiovascular hospitalizations during the period. A reduction was observed in the number of clinical hospitalizations, but spending on care for patients with HF increased by 32%, with HF responsible for the majority of costs related to clinical hospitalizations for cardiovascular diseases.[4]

The therapeutic proposals described in this article are considered the essential pillars of treatment of HF with reduced ejection fraction (HFREF) and are founded scientifically in the most important studies of HFREF, targeting clinical applicability in a simple and concise manner, to improve treatment of patients with this diagnosis.

Renin-angiotensin-aldosterone System (RAAS) – ACEI, ARB, and MRA

The RAAS is activated early and intensely in HFREF. In patients with ventricular dysfunction causing reduced cardiac output, there is sympathetic activation with peripheral vasoconstriction and reduced renal perfusion, stimulating renin production which metabolizes angiotensinogen produced in the liver into angiotensin I.

Keywords

Heart Failure; Angiotensin II Type 1 Receptor Blockers; Mineralocorticoid Receptor Antagonists; Sodium-Glucose Transporter 2 Inhibitors.

Mailing Address: Marcely Gimenes Bonatto •
Av. Silva Jardim 2939, apt 81. Postal Code 80240-020, Curitiba, PR – Brazil
E-mail: marcelybonatto@gmail.com
Manuscript received January 31, 2022, revised manuscript February 01, 2022, accepted February 16, 2022

DOI: https://doi.org/10.36660/abchf.20220003

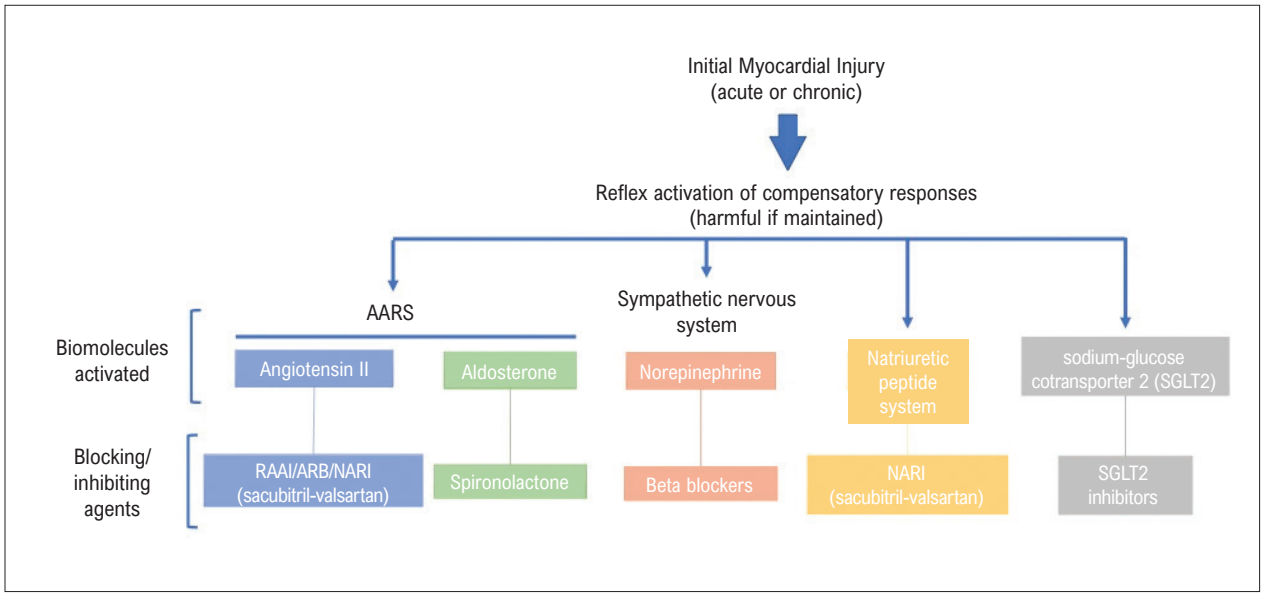


Figure 1 – *The pillars of treatment for HFREF.*

Angiotensin-converting enzyme (ACE) is responsible for transforming angiotensin I into angiotensin II. This, in turn, is a potent vasoconstrictor, provoking increased arterial blood pressure, increased afterload, sympathetic activation, tachycardia, and renal vasoconstriction with retention of salt and water, with increased preload and, as a result, recovery of cardiac output.

However, over time, this stimulation transitions from compensatory to harmful, provoking cellular hypertrophy and myocardial apoptosis and fibrosis and stimulating disease progression.

Modulators of this system include the RAAIs, which act to inhibit conversion of angiotensin I into angiotensin II and the ARBs which act to selectively block the AT1 angiotensin II receptor. The ARBs do not interfere in bradykinin degradation, reducing one of the most intolerable side effects of the IECAs, which is coughing.

Activation of angiotensin II also stimulates release of aldosterone by the suprarenal glands, provoking retention of salt and water (increasing the volume of blood in circulation) and increasing arterial blood pressure. These responses are initially important to restore cardiac output, but as time passes they lead to hypervolemia, symptoms of congestion, increased filling pressures, direct cellular injury by increased oxidative stress, collagen in the extracellular matrix, and myocardial and vascular hypertrophy and fibrosis, resulting in progression of cardiac remodeling.

Modulation of the effects of aldosterone is achieved using MRA antagonists. The only MRA available in Brazil is sprinolactone, a drug with strong antimineralocorticoid activity, moderate antiandrogenic activity, and mild steroidogenesis inhibition. This drug acts to competitively inhibit sodium-aldosterone-dependent potassium exchange channels, provoking natriuresis with a high concentration of sodium and retention of potassium. Use of MRAs is very important in HFREF to reduce mortality, morbidity, and hospital admissions and is complementary to blocking the RAAS with ACEI or ARB.[5-7]

These medications were tested in a series of clinical studies that demonstrated their importance in treatment of HFREF with benefits in terms of reduction of morbidity and mortality and improved patient quality of life. (Table 1: ACEI; Table 2:ARB; Table 3:MRA).

Autonomic nervous system (ANS) – beta blockers

Activation of the ANS is one of the body's first responses after cardiac output reduces, increasing production and release of catecholamines. This results in increases in heart contractility and rate, systemic vasoconstriction, reduced venous complacency, thereby maintaining higher cardiac output. The parasympathetic system is thus attenuated while the sympathetic system is hyperactivated. Over the long term, sympathetic hyperactivity can increase myocardial O2 demand, predisposing to ventricular arrhythmia and activating hypertrophy and apoptosis signaling pathways, linked or not to the RAAS, and setting up a vicious circle of HF exacerbation. Prolonged activation of this system leads to reduction of beta-adrenergic receptors in the heart, reducing its capacity for chronotropism. The concentration of norepinephrine is directly proportional to the severity of cardiac dysfunction and inversely proportional to survival. Its major role in the pathophysiology and progression of HFREF makes ANS a target of treatment for the disease.[5,18,19]

One of the most important pillars of HF treatment is beta blockers, which modify the natural history of the disease and can reduce cardiovascular mortality by 30%,[14] with reduction of morbidity and reverse remodeling of the LV. They should be initiated as early as possible in patients

Table 1 – Principal studies investigating use of ICEI in HFREF

ACEI studies	CONSENSUS[8]	SOLVD treatment[9]	SOLVD prevention[10]
Year	1987	1991	1992
Intervention	Enalapril x placebo	Enalapril x placebo	Enalapril x placebo
Period (follow-up)	1985-1986 (188 days)	1986-1989 (4.4 months)	1986-1990 (37.4 months)
Nº of patients	253	2569	2737
Characteristics of the population	NYHA IV HF with cardiomegaly	NYHA I - IV HF LVEF ≤ 35%	NYHA I and II HF LVEF ≤ 35%
Primary outcome	Death from all causes	Death from all causes	Death from all causes
Results	Enalapril demonstrated a 40% reduction in total mortality in 6 months and 31% in 12 months in relation to placebo	Enalapril demonstrated a 16% reduction in total mortality and 26% in death or hospital admissions for HF in relation to placebo	Enalapril was not different to placebo for mortality, but reduced risk of death or hospital admission for HF by 20%

ACEI: Angiotensin-converting enzyme inhibitor; HF: Heart failure; NYHA: New York Heart Association; LVEF: Left ventricle ejection fraction.

Table 2 – Principal studies investigating ARB in in HFREF

ARB studies	ELITE II [11]	Val-HeFT [12]	CHARM- Added[13]	CHARM- Alternative[14]
Year	2000	2001	2003	2003
Intervention	Losartan x captopril	Valsartan x placebo	Candesartan x placebo	Candesartan x placebo
Period (follow-up)	1997-1998 (18.5 months)	1997-1999 (23 months)	1999-1999 (41 months)	1999-2001 (33.7 months)
Nº of patients	3152	5010	2548	2028
Characteristics of the population	NYHA II-IV HF LVEF ≤ 40% > 60 years	NYHA II-IV HF LVEF < 40% 93% taking ACEI	NYHA II-IV HF LVEF ≤ 40% All patients taking ACEI	NYHA II-IV HF LVEF ≤40% No patients taking ACEI
Primary outcome	Death from all causes	Death from all causes	Cardiovascular death and hospital admissions for HF	Cardiovascular death and hospital admissions for HF
Results	There were no significant differences in mortality from all causes or sudden death between the two treatment groups.	18% reduction in the composite outcome (death, cardiac arrest with resuscitation, hospital admissions for HF, need for IV vasodilators or inotropics) and improvement in quality of life in relation to placebo, especially in the subset not taking ACEI or beta blockers.	Addition of Candesartan reduced the primary outcome by 15% in relation to placebo, in patients with HFREF already taking ACEI.	Candesartan reduced the primary outcome by 23% in relation to placebo.

ARB: Angiotensin Receptor Blocker; HF: Heart failure; NYHA: New York Heart Association; LVEF: Left ventricle ejection fraction; IV: intravenous.

diagnosed with HF with reduced ejection fraction who are sTable and euvolemic.

Studies that have investigated the effects of this therapy in patients with HF with reduced ejection fraction can be consulted in Table 4.

Natriuretic peptides system (NPS) –NRAI

The natriuretic peptides (NP) are biomarkers produced by the atria and ventricles when there is ventricular wall stress and myocardial fibers are stretched. Natriuretic peptides, and type B (BNP) in particular, have a complex set of effects, affecting kidneys, blood vessels, heart, endocrine functions, cell growth, and cardiac remodeling. In the renal system, they induce increased glomerular filtration and reduced tubular reabsorption of sodium and water, protecting the kidney and increasing natriuresis. In the cardiovascular system, they provoke vasodilation and have anti-remodeling effects via local regulation of collagen synthesis, with reduction of cellular hypertrophy and fibrosis. They therefore act to antagonize the effects provoked by sympathetic activation and by the RAAS as the body seeks to achieve homeostasis.[25]

Since elevated levels reflect increased filling pressure and ventricular wall stress, natriuretic peptides – particularly BNP and NT-proBNP – can be used in differential diagnosis of dyspnea. Highly elevated levels

Table 3 – Principal studies investigating use of MRA in HFREF

MRA Studies	RALES[15]	EPHESUS[16]	EMPHASIS-HF [17]
Year	1999	2003	2010
Intervention	Sprinolactone x placebo	Eplerenone x placebo	Eplerenone x placebo
Period (follow-up)	1995-1996 (2 years)	1999-2001 (1 year and 4 months)	2006-2010 (21 months)
Nº of patients	1663	6642	2737
Characteristics of the population	NYHA III or IV HF LVEF ≤ 35%	Recent AMI (3-14 days) LVEF ≤40% Symptoms of HF or DM	NYHA II HF LVEF ≤ 30%
Primary outcome	Death from all causes	Death from all causes	Cardiovascular death and hospital admissions for HF
Results	Sprinolactone was superior to placebo, reducing the primary outcome by 30%, cardiovascular deaths by 31%, and hospital admissions for cardiovascular causes by 30%.	Eplerenone was superior to placebo, reducing the primary outcome by 15%. There was a 21% reduction in sudden death from cardiac causes in the eplerenone group.	Eplerenone was superior to placebo, reducing the primary outcome by 34%. It also reduced total mortality and sudden deaths.

MRA: Mineralocorticoid receptor antagonists; HF: Heart failure; NYHA: New York Heart Association; LVEF: Left ventricle ejection fraction; AMI: acute myocardial infarction; DM: diabetes mellitus.

Table 4 – Principal studies investigating beta blockers in HFREF and their effects in this population

Beta blocker studies	US CARVEDILOL[20]	CIBIS II[21]	MERIT-HF[22]	COPERNICUS[23]	SENIOR[24]
Year	1996	1999	1999	2001	2005
Intervention	Carvedilol x placebo	Bisoprolol x placebo	Metoprolol succinate x placebo	Carvedilol x placebo	Nebivolol x placebo
Period (follow-up)	1993-1995 (12 months)	2001-2003 (1.3 years)	1997-1998 (1 year)	1997-2000 (10.4 months)	2000-2002 (21 months)
Nº of patients	1094	2647	3991	2289	2128
Characteristics of the population	Symptomatic HF for at least 3 months LVEF ≤ 35%	Ambulatory, NYHA III-IV LVEF ≤ 35%	NYHA II-IV LVEF ≤ 40%	HF CF IV for 2 months LVEF < 25% Euvolemia Optimized clinical treatment	Age ≥ 70 years History of hospital admissions in the last year with discharge diagnosis of HF LVEF ≤ 35%
Primary outcome	Death from all causes	Death from all causes	Death from all causes and death from all causes + hospital admissions from all causes	Death from all causes	Death from all causes or cardiovascular hospital admissions
Results	Carvedilol reduced the primary outcome in 65% of the patients. There was also a 27% reduction in the risk of hospital admissions for cardiovascular causes and a 38% reduction in the combined risk of hospital admissions or death	Bisoprolol reduced the primary outcome by 32% compared with placebo, in addition to reducing hospital admissions for any cause by 20% and cardiovascular mortality by 29%.	Metoprolol reduced the primary outcome by 34%, cardiovascular mortality by 38%, cardiac sudden death by 41%, and mortality due to HF progression by 49%. The study was terminated because of the large clinical benefit of metoprolol compared with placebo.	Carvedilol reduced the primary outcome by 35% Carvedilol reduced the combined risk of death or hospital admissions for any cause by 27% and the combined risk of death or hospital admissions for HF by 31%.	Nebivolol proved effective for treatment of HF in elderly patients, achieving a 14% reduction in cardiovascular events compared with placebo. There was no difference in mortality from all causes.

HF: Heart failure; FC: functional class; HF: Heart failure; LVEF: Left ventricle ejection fraction.

make a diagnosis of HF likely and low levels have a high negative predictive power for ruling out the disease. However, it is important to consider body mass index, renal function, and atrial fibrillation rhythm when interpreting these values.[4,26,27]

This potential to promote counter-regulation of the sympathetic system and the RAAS, with desirable effects in HFREF (especially vasodilation and natriuresis), prompted development of SACUBITRIL/VALSARTAN, a new class of drug (neprilysin and angiotensin receptor inhibitors - NARI) that combines Sacubitril, an inhibitor of neprilysin (the enzyme responsible for degradation of endogenous BNP), with valsartan (an angiotensin II receptor blocker). The PARADIGM study[28,29] compared this drug with RAAS block using enalapril, demonstrating an important reduction in the clinical outcomes mortality and sudden death and also a reduction in hospitalizations for HF and improved quality of life. The PROVE HF study[21] correlated the reduction in NT-ProBNP with the capacity to provoke reverse remodeling. After 12 months taking Sacubitril/valsartan, a 9.4% mean improvement was observed in ejection fraction in relation to baseline with important reverse remodeling in LV and LA dimensions. Several studies have demonstrated an important impact of the process of ventricular function recovery on reduction of hospitalizations, cardiovascular mortality, sudden death, and overall mortality among patients taking this drug class.

Studies that have investigated the effects of this treatment in patients with HF with reduced ejection fraction are described in Table 5.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors – Dapaglifozin and Empagliflozin

Although SGLT2 inhibitors have been primarily used in treatment of diabetes mellitus because of their mechanism of inhibition of glucose resorption in the proximal convoluted tubule, provoking glycosuria and consequent reduction of glycemic levels, studies of cardiovascular outcomes have demonstrated clinical benefits in studies with SGLT2 inhibitors, reducing hospitalizations for HF and cardiovascular death. It should be noted that these benefits were observed in patients with and without DM.[32-35]

The mechanisms that confer the optimistic results of this drug class in patients with HF are not yet fully explained. Mechanisms that can be listed include improved left ventricle parietal tension due to reduced preload (thanks to natriuresis and osmotic diuresis) and afterload (due to improved endothelial function and reduced arterial blood pressure), improved metabolism bioenergetics of the cardiomyocytes, reduced cardiac necrosis and fibrosis, changes to cytokines, and reduced epicardial fat.[32,35]

Studies that have investigated the effects of this treatment in patients with HF with reduced ejection fraction can be seen in Table 6.

Figure 2 summarizes the benefits of each drug class according to the scientific evidence on the principal outcomes sought in treatment for HFREF: reduction of mortality, reduction of sudden death,[38,39] improvement of symptoms and quality of life, reduction of hospital admissions, and promotion of reverse remodeling.[31,40-44]

In view of this evidence, it is important to understand that pharmacological treatment of HFREF should be given using a combination of different drugs that act on different systems, achieving the greatest reduction of risk possible. There is evidence that treatment with a combination of NARI, beta blocker, MRA, and SGLT2I is capable of provoking important reductions in events (cardiovascular death or hospital admissions for HF) and increases in survival when compared with treatment using only ACEI or ARB in conjunction with a beta blocker. It is estimated that this benefit can be translated into an increase in event-free life of 2.7-8.3 years and increased life expectancy of 1.4 to 6.3 years, depending on the age of the individual.[45]

Drugs used in treatment of HFREF and their initial and target doses are summarized[1,5] in Table 7

Conclusions

Pharmacological treatment of HFREF has been changing over recent years, involving new systems and with discovery of new classes of medications, having an important impact on clinical outcomes. Understanding of the individual benefits and the potential for synergy of these drugs, targeting the greatest reduction in morbidity and mortality, is essential to choosing the best treatment.

Author Contributions

Conception and design of the research: Bonatto MG; Acquisition of data and Writing of the manuscript: Bonatto MG, Coiradas AO; Critical revision of the manuscript for intellectual contente: Moura LAZ.

Potential Conflict of Interest

Dra. Marcely Gimenes Bonatto: speaker Novartis e Astra Zeneca.

Dra. Lídia Ana Zytynski Moura: speaker Novartis e Astra Zeneca.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Table 5 – Principal studies investigating NARI in HFREF

NARI studies	PARADIGM-HF[28]	PIONEER- HF [30]	PROVE-HF[31]
Year	2014	2019	2019
Intervention	Sacubitril/Valsartan x Enalapril	Sacubitril/Valsartan x Enalapril	To evaluate whether variation in NT-proBNP in patients with HFREF treated with Sacubitril/valsartan correlated with variation in cardiac volume and function.
Period (follow-up)	2009-2012 (27 months)	2016-2018 (2 months)	2016-2018 (12 months)
Nº of patients	8442	887	794
Characteristics of the population	NYHA II-IV HF LVEF ≤ 35% BNP 150 ≥ or NTproBNP ≥ 600pg/ml; or BNP ≥ 100pg/ml or NTproBNP ≥ 400pg/ml if admitted to hospital for HF less than 1 year previously	LVEF ≤ 40% NT-proBNP ≥ 1600pg/ml or BNP ≥ 400 pg/ml Primary diagnosis of decompensated HF, including signs and symptoms of volume overload	NYHA II-IV HF LVEF ≤ 40%
Primary outcome	Cardiovascular mortality or first hospital admissions for HF	Mean time-proportional change in NT-proBNP concentration from outset to weeks 4 and 8	Correlation between variation in concentration of NT-proBNP and cardiac remodeling
Results	The study was terminated prematurely because of the important benefit of sacubitril/ valsartan observed, with a 20% reduction in the composite primary outcome, 20% reduction in cardiovascular death, and 21% reduction in hospitalizations.	The mean reduction in NT-proBNP was significantly higher in the Sacubitril/valsartan group than in the enalapril group (-46.7% and -25.3%, respectively). There was a 46% reduction in the composite exploratory outcome of death, hospital re-admissions for HF, implantation of left ventricular assist devices, or heart transplantation.	The reduction in NT-proBNP concentration was correlated with improvement in markers of cardiac volume and function at 6 and 12 months.

NARI: Neprilysin and Angiotensin Receptor Inhibitor; HF: Heart failure; NYHA: New York Heart Association; LVEF: Left ventricle ejection fraction. NT-proBNP: N-terminal pro b-type natriuretic peptide; HFREF: heart failure with reduced ejection fraction.

Table 6 – Principal studies of SGLT2 inhibitors in HFREF

SGLT-2 inhibitors	DAPA-HF[36]	EMPERROR - REDUCED [37]
Year	2019	2020
Intervention	Dapaglifozin x placebo	Empagliflozin x placebo
Period (follow-up)	2017-2018 (18.2 months)	2017-2019 (16 months)
Nº of patients	4744	3730
Characteristics of the population	NYHA II-IV HF LVEF ≤ 40% with or without DM2 NTproBNP ≥ 600pg/ml; or NTproBNP ≥ 400pg/ml if admitted to hospital for HF within 1 year. If AF or atrial flutter > NTproBNP ≥ 900pg/ml	NYHA II-IV HF LVEF ≤ 40% with or without DM2 NT-proBNP ≥ 2500pg/ml if EF 36-40%; NT-proBNP ≥ 1000pg/ml if FE 31-35%; NT-proBNP ≥ 600pg/ml if FE ≤30%;
Primary outcome	Worsening of HF (urgent care requiring hospital admission or use of IV therapy) or cardiovascular death	Cardiovascular death or hospital admissions for HF
Results	Dapaglifozin reduced the primary outcome by 26% and reduced mortality from all causes by 17% irrespective of DM2	Empagliflozin reduced the primary outcome by 25% compared with placebo. Effects were similar in patients with or without DM2.

SGLT2: sodium-glucose cotransporter 2; HF: Heart failure; NYHA: AF: atrial fibrillation; New York Heart Association; LVEF: Left ventricle ejection fraction; IV: intravenous; DM2: Type 2 Diabetes mellitus.

Figure 2 – *Benefits of pharmacological treatment of HFREF by drug classes. ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; MRA: Mineralocorticoid receptor antagonists; NARI: Neprilysin and angiotensin receptor inhibitor; SGLT2I: SGLT2: Sodium-glucose cotransporter 2 inhibitors.*

Table 7 – Drugs used in HFREF treatment

Drug	Initial dose	Target dose
ACEI		
Captopril	6.25mg – 3x/day	50mg – 3x/day
Enalapril	2.5mg – 2x/day	10 - 20mg – 2x/day
Ramipril	1.25 - 2.5mg – 1x/day	10mg – 1 x/day
Lisinopril	2.5 - 5mg – 1x/day	20 - 40mg – 1x/day
Perindopril	2mg – 1x/day	8 - 16mg – 1x/day
ARB		
Candesartan	4 - 8mg – 1x/day	32mg – x/day
Losartan	25 - 50mg – 1x/day	100 -150mg – 2 x/day
Valsartan	40 - 80mg – 1x/day	320mg – 1x/day
MRA		
Sprinolactone	25mg – 1x/day	25mg – 1x/day 50mg – 1x/day in refractory HF cases
NARI		
Sacubitril/Valsartan	24/26mg – 2x/day	97/103mg – 2x/day
Beta blocker		
Carvedilol	3.125mg -2x/day	25mg – 2x/day 50mg-2x/day se > 85kg
Metoprolol succinate	25mg – 1x/day	200mg – 1x/day
Bisoprolol	1.25mg -1x/day	10mg – 1x/day
SGLT2 inhibitors		
Dapaglifozin	10mg – 1x/day	10mg – 1x/day
Empagliflozin	10mg – 1x/day	10mg – 1x/day

ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; MRA: Mineralocorticoid receptor antagonists; NARI: Neprilysin and angiotensin receptor inhibitor; SGLT2I: SGLT2: Sodium-glucose cotransporter 2 inhibitors.

References

1. Marcondes-Braga FG, Moura LAZ, Issa VS, Vieira JL, Rohde LE, Simões MV, et al. Emerging Topics Update of the Brazilian Heart Failure Guideline - 2021. Arq Bras Cardiol. 2021;116(6):1174-212. doi: 10.36660/abc.20210367.
2. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, et al. Heart Disease and Stroke Statistics-2020 Update: A Report from the American Heart Association. Circulation. 2020;141(9):139-596. doi: 10.1161/CIR.0000000000000757.
3. Rohde LEP, Montera MW, Bocchi EA, Clausell NO, Albuquerque DC, Rassi S, et al. Diretriz Brasileira de Insuficiência Cardíaca Crônica e Aguda. Arq Bras Cardiol. 2018 Sep;111(3):436-539. doi: 10.5935/abc.20180190.
4. Oliveira GMM, Brant LCC, Polanczyk CA, Malta DC, Biolo A, Nascimento BR, et al. Estatística Cardiovascular – Brasil 2021. Arq. Bras. Cardiol. 2022;118(1):115-373.
5. Figueiredo Neto JA. et.al. Insuficiência Cardíaca DEIC-SBC. São Paulo: Manole; 2021.
6. Hartupee J, Mann DL. Neurohormonal Activation in Heart Failure with Reduced Ejection Fraction. Nat Rev Cardiol. 2017;14(1):30-8. doi: 10.1038/nrcardio.2016.163.
7. Packer M. The Neurohormonal Hypothesis: A Theory to Explain the Mechanism of Disease Progression in Heart Failure. J Am Coll Cardiol. 1992;20(1):248-54. doi: 10.1016/0735-1097(92)90167-l.
8. CONSENSUS Trial Study Group. Effects of Enalapril on Mortality in Severe Congestive Heart Failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med. 1987;316(23):1429-35. doi: 10.1056/NEJM198706043162301.
9. Bowling CB, Sanders PW, Allman RM, Rogers WJ, Patel K, Aban IB, et al. Effects of enalapril in systolic heart failure patients with and without chronic kidney disease: insights from the SOLVD Treatment trial. Int J Cardiol. 2013 Jul 15;167(1):151-6. doi: 10.1016/j.ijcard.2011.12.056.
10. Das SR, Drazner MH, Yancy CW, Stevenson LW, Gersh BJ, Dries DL. Effects of Diabetes Mellitus and Ischemic Heart Disease on the Progression from Asymptomatic Left Ventricular Dysfunction to Symptomatic Heart Failure: A Retrospective Analysis from the Studies of Left Ventricular Dysfunction (SOLVD) Prevention Trial. Am Heart J. 2004;148(5):883-8. doi: 10.1016/j.ahj.2004.04.019.
11. Pitt B, Poole-Wilson PA, Segal R, Martinez FA, Dickstein K, Camm AJ, et al. Effect of Losartan Compared with Captopril on Mortality in Patients with Symptomatic Heart Failure: Randomised Trial--the Losartan Heart Failure Survival Study ELITE II. Lancet. 2000;355(9215):1582-7. doi: 10.1016/s0140-6736(00)02213-3.
12. Carson P, Tognoni G, Cohn JN. Effect of Valsartan on hospitalization: Results from Val-HeFT. J Card Fail. 2003;9(3):164-71. doi: 10.1054/jcaf.2003.22.
13. McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, et al. Effects of Candesartan in Patients with Chronic Heart Failure and Reduced Left-Ventricular Systolic Function Taking Angiotensin-Converting-Enzyme Inhibitors: The CHARM-Added Trial. Lancet. 2003;362(9386):767-71. doi: 10.1016/S0140-6736(03)14283-3.
14. Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, et al. Effects of Candesartan in Patients with Chronic Heart Failure and Reduced Left-ventricular Systolic Function Intolerant to Angiotensin-Converting-Enzyme Inhibitors: The CHARM-Alternative Trial. Lancet. 2003;362(9386):772-6. doi: 10.1016/S0140-6736(03)14284-5.
15. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999;341(10):709-17. doi: 10.1056/NEJM199909023411001.
16. Pitt B, Williams G, Remme W, Martinez F, Lopez-Sendon J, Zannad F, et al. The EPHESUS Trial: Eplerenone in Patients with Heart Failure Due to Systolic Dysfunction Complicating Acute Myocardial Infarction. Eplerenone Post-AMI Heart Failure Efficacy and Survival Study. Cardiovasc Drugs Ther. 2001;15(1):79-87. doi: 10.1023/a:1011119003788.
17. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, et al. Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms. N Engl J Med. 2011;364(1):11-21. doi: 10.1056/NEJMoa1009492.
18. Floras JS, Ponikowski P. The Sympathetic/Parasympathetic Imbalance in Heart Failure with Reduced Ejection Fraction. Eur Heart J. 2015;36(30):1974-82. doi: 10.1093/eurheartj/ehv087.
19. Grassi G, Quarti-Trevano F, Esler MD. Sympathetic Activation in Congestive Heart Failure: An Updated Overview. Heart Fail Rev. 2021;26(1):173-82. doi: 10.1007/s10741-019-09901-2.
20. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, et al. The Effect of Carvedilol on Morbidity and Mortality in Patients with Chronic Heart Failure. U.S. Carvedilol Heart Failure Study Group. N Engl J Med. 1996;334(21):1349-55. doi: 10.1056/NEJM199605233342101.
21. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): A Randomised Trial. Lancet. 1999;353(9146):9-13.
22. Effect of Metoprolol CR/XL in Chronic Heart Failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet. 1999;353(9169):2001-7.
23. Packer M, Fowler MB, Roecker EB, Coats AJ, Katus HA, Krum H, et al. Effect of Carvedilol on the Morbidity of Patients with Severe Chronic Heart Failure: Results of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study. Circulation. 2002;106(17):2194-9. doi: 10.1161/01.cir.0000035653.72855.bf.
24. Flather MD, Shibata MC, Coats AJ, Van Veldhuisen DJ, Parkhomenko A, Borbola J, et al. Randomized Trial to Determine the Effect of Nebivolol on Mortality and Cardiovascular Hospital Admission in Elderly Patients with Heart Failure (SENIORS). Eur Heart J. 2005;26(3):215-25. doi: 10.1093/eurheartj/ehi115.
25. Brunner-La Rocca HP, Sanders-van Wijk S. Natriuretic Peptides in Chronic Heart Failure. Card Fail Rev. 2019;5(1):44-9. doi: 10.15420/cfr.2018.26.1.
26. Maisel AS, Duran JM, Wettersten N. Natriuretic Peptides in Heart Failure: Atrial and B-type Natriuretic Peptides. Heart Fail Clin. 2018;14(1):13-25. doi: 10.1016/j.hfc.2017.08.002.
27. Mueller C, McDonald K, de Boer RA, Maisel A, Cleland JGF, Kozhuharov N, et al. Heart Failure Association of the European Society of Cardiology Practical Guidance on the Use of Natriuretic Peptide Concentrations. Eur J Heart Fail. 2019;21(6):715-31. doi: 10.1002/ejhf.1494.
28. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-Neprilysin Inhibition Versus Enalapril in Heart Failure. N Engl J Med. 2014;371(11):993-1004. doi: 10.1056/NEJMoa1409077.
29. Desai AS, McMurray JJ, Packer M, Swedberg K, Rouleau JL, Chen F, et al. Effect of the Angiotensin-Receptor-Neprilysin Inhibitor LCZ696 Compared with Enalapril on Mode of Death in Heart Failure Patients. Eur Heart J. 2015;36(30):1990-7. doi: 10.1093/eurheartj/ehv186.
30. Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, et al. Angiotensin-Neprilysin Inhibition in Acute Decompensated Heart Failure. N Engl J Med. 2019;380(6):539-48. doi: 10.1056/NEJMoa1812851.
31. Januzzi JL, Butler J, Fombu E, Maisel A, McCague K, Piña IL, et al. Rationale and Methods of the Prospective Study of Biomarkers, Symptom Improvement, and Ventricular Remodeling During Sacubitril/Valsartan Therapy for Heart Failure (PROVE-HF). Am Heart J. 2018;199:130-6. doi: 10.1016/j.ahj.2017.12.021.

32. Bocchi EA, Biolo A, Moura LZ, Figueiredo Neto JA, Montenegro CEL, Albuquerque DC. Emerging Topics in Heart Failure: Sodium-Glucose Co-Transporter 2 Inhibitors (SGLT2i) in HF. Arq Bras Cardiol. 2021;116(2):355-8. doi: 10.36660/abc.20210031.

33. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015;373(22):2117-28. doi: 10.1056/NEJMoa1504720.

34. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, et al. SGLT2 Inhibitors for Primary and Secondary Prevention of Cardiovascular and Renal Outcomes in Type 2 Diabetes: A Systematic Review and Meta-Analysis of Cardiovascular Outcome Trials. Lancet. 2019;393(10166):31-9. doi: 10.1016/S0140-6736(18)32590-X X.

35. Verma S, McMurray JJV. SGLT2 Inhibitors and Mechanisms of Cardiovascular Benefit: A State-of-the-Art Review. Diabetologia. 2018;61(10):2108-17. doi: 10.1007/s00125-018-4670-7.

36. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019;381(21):1995-2008. doi: 10.1056/NEJMoa1911303.

37. Packer M, Anker SD, Butler J, Filippatos G, Ferreira JP, Pocock SJ, et al. Empagliflozin in Patients with Heart Failure, Reduced Ejection Fraction, and Volume Overload: EMPEROR-Reduced Trial. J Am Coll Cardiol. 2021;77(11):1381-92. doi: 10.1016/j.jacc.2021.01.033.

38. Al-Gobari M, Al-Aqeel S, Gueyffier F, Burnand B. Effectiveness of Drug Interventions to Prevent Sudden Cardiac Death in Patients with Heart Failure and Reduced Ejection Fraction: An Overview of Systematic Reviews. BMJ Open. 2018;8(7):e021108. doi: 10.1136/bmjopen-2017-021108.

39. Curtain JP, Docherty KF, Jhund PS, Petrie MC, Inzucchi SE, Køber L, et al. Effect of Dapagliflozin on Ventricular Arrhythmias, Resuscitated Cardiac Arrest, or Sudden Death in DAPA-HF. Eur Heart J. 2021;42(36):3727-38. doi: 10.1093/eurheartj/ehab560.

40. Konstam MA, Rousseau MF, Kronenberg MW, Udelson JE, Melin J, Stewart D, et al. Effects of the Angiotensin Converting Enzyme Inhibitor Enalapril on the Long-Term Progression of Left Ventricular Dysfunction in Patients with HEART FAILure. SOLVD Investigators. Circulation. 1992;86(2):431-8. doi: 10.1161/01.cir.86.2.431.

41. Tsutamoto T, Wada A, Maeda K, Mabuchi N, Hayashi M, Tsutsui T, et al. Effect of Spironolactone on Plasma Brain Natriuretic Peptide and Left Ventricular Remodeling in Patients with Congestive Heart Failure. J Am Coll Cardiol. 2001;37(5):1228-33. doi: 10.1016/s0735-1097(01)01116-0.

42. Hall SA, Cigarroa CG, Marcoux L, Risser RC, Grayburn PA, Eichhorn EJ. Time Course of Improvement in Left Ventricular Function, Mass and Geometry in Patients with Congestive Heart Failure Treated with Beta-Adrenergic Blockade. J Am Coll Cardiol. 1995;25(5):1154-61. doi: 10.1016/0735-1097(94)00543-y.

43. Lee MMY, Brooksbank KJM, Wetherall K, Mangion K, Roditi G, Campbell RT, et al. Effect of Empagliflozin on Left Ventricular Volumes in Patients with Type 2 Diabetes, or Prediabetes, and Heart Failure With Reduced Ejection Fraction (SUGAR-DM-HF). Circulation. 2021;143(6):516-25. doi: 10.1161/CIRCULATIONAHA.120.052186.

44. Santos-Gallego CG, Vargas-Delgado AP, Requena-Ibanez JA, Garcia-Ropero A, Mancini D, Pinney S, et al. Randomized Trial of Empagliflozin in Nondiabetic Patients with Heart Failure and Reduced Ejection Fraction. J Am Coll Cardiol. 2021;77(3):243-55. doi: 10.1016/j.jacc.2020.11.008.

45. Vaduganathan M, Claggett BL, Jhund PS, Cunningham JW, Ferreira JP, Zannad F, et al. Estimating Lifetime Benefits of Comprehensive Disease-modifying Pharmacological Therapies in Patients with Heart Failure with Reduced Ejection Fraction: A Comparative Analysis of Three Randomised Controlled Trials. Lancet. 2020;396(10244):121-8. doi: 10.1016/S0140-6736(20)30748-0.

HFREF Pharmacological Treatment Sequencing: The Traditional Approach

João Manoel Rossi Neto,[1] Raphael Machado Rossi,[1] Marco Aurelio Finger,[1] Carolina Casadei dos Santos[1]
Instituto Dante Pazzanese de Cardiologia,[1] São Paulo, SP – Brazil

The traditional approach to sequencing

This approach respects the historical introduction of drugs studied and proven by randomized clinical trials (RCTs) and has its use approved by all guidelines.[1–3] It is important to note that all RCTs on heart failure with reduced ejection fraction (HFrEF) have used this sequencing approach, and when a new drug is tested, it is added to optimized standard therapy. This reinforces the need to maintain triple therapy with a beta-blocker (BB), an angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB), and a mineralocorticoid receptor antagonist (MRA). Therefore, this triad is recommended as a key therapy for HFrEF unless drugs are contraindicated or not tolerated.

Angiotensin receptor-neprilysin inhibitors (ARNis; sacubitril/valsartan) should replace ACEis in patients who remain symptomatic despite the triad and may also be considered first-line therapy instead of ACEis (Figure 1). The maximum recommended doses (MRDs) of these drugs are described in the Brazilian Society of Cardiology guidelines.[4]

The sodium-glucose cotransporter 2 inhibitors (SGLT2i) dapagliflozin and empagliflozin (both at starting and target doses of 10 mg once daily), when added to the described therapy (Figure 1), reduced the risk of cardiovascular death and worsening heart failure (HF) in HFrEF, regardless of whether the patient had diabetes.[2,3]

Therefore, these four drugs, ARNi or ACEi/ARB + BB + spironolactone + SGLT2i, are recommended in all guidelines following the steps described above.[1–3] Combination of medications that have had an impact on morbidity is also possible, and the choice of these additional therapies should consider the profile of each patient (Figure 1).[2]

A period (3-6 months) for clinical and functional reassessment aims to optimize therapy in an environment favorable to a progressive increase in MRD/tolerated dose. Side effects should be observed, and possible strategies should be used to minimize or avoid these undesirable effects (Figure 1).[2]

The most current evidence for MRD in the guidelines comes from the CHAMP-HF (Change the Management of Patients with Heart Failure)[5] registry, in which the target dose of ACEi/ARNi/ARB and BB was associated with lower mortality, lower HF hospitalization, and fewer patient-reported outcomes, supporting the benefits of MRD in routine clinical practice. The initiation of sacubitril/valsartan, even at the target dose, did not lead to further discontinuation/dose reduction of other essential therapies.[6] The 97/103 or 49/51 mg dose had a lower mortality/hospitalization rate for HF versus the 24/26 mg dose.[7] High-dose BB showed better clinical outcomes.[8] Titration protocol led to high-dose medical therapy and improved left ventricular ejection fraction in patients with recent-onset HFrEF.[9]

The nontraditional approach to sequencing

Recently, nontraditional sequencing approaches (NTSAs) have been proposed. Quadruple therapy should be started as soon as possible, simultaneously, at low doses, using late titration over a short-term period of 4 weeks to 43 days.[10–16] Despite the strategy[12] having a strong theoretical and logical foundation, targeting several different pathophysiological steps in a quick sequence, and seeking to break clinical inertia/treat HFrEF with the utmost urgency,[11,12] the NTSA has never been actually tested. There is no RCT to support this proposal, nor is there full agreement on how quickly and in what order this sequencing should be done or whether this strategy will increase patient compliance. There are only the opinions of renowned investigators, retrospective analyses, and statistical models.

The NTSA can make clinical evaluation difficult, cause side effects (despite the claim to reduce these effects), favor the inertia of therapeutic optimization ("My patient is stable with underdosage"), and cause the continuous risks of sudden death and disease progression to be "forgotten".[17–19] Some investigators may have more laboratory experience and do not deal with treatment barriers on a day-to-day basis; there is a large difference between the "theoretical" patient and the "real" patient.

For these reasons, the NTSA has not yet been explicitly incorporated into current HFrEF guidelines, and RCTs are expected to verify its effectiveness and safety.

Keywords

Medication Therapy Management, Heart Failure, Ventricular Ejection Fraction

Mailing Address: João Manoel Rossi Neto •
Ambulatório de Disfunção Ventricular e Transplante de Coração – Av. Dante Pazzanese, 500. Postal Code 04012-909, Ibirapeura, São Paulo, SP – Brazil
E-mail: jmrossi@sti.com.br
Manuscript received January 13, 2022, revised manuscript February 01, 2022, accepted February 14, 2022

DOI: https://doi.org/10.36660/abchf.20220004

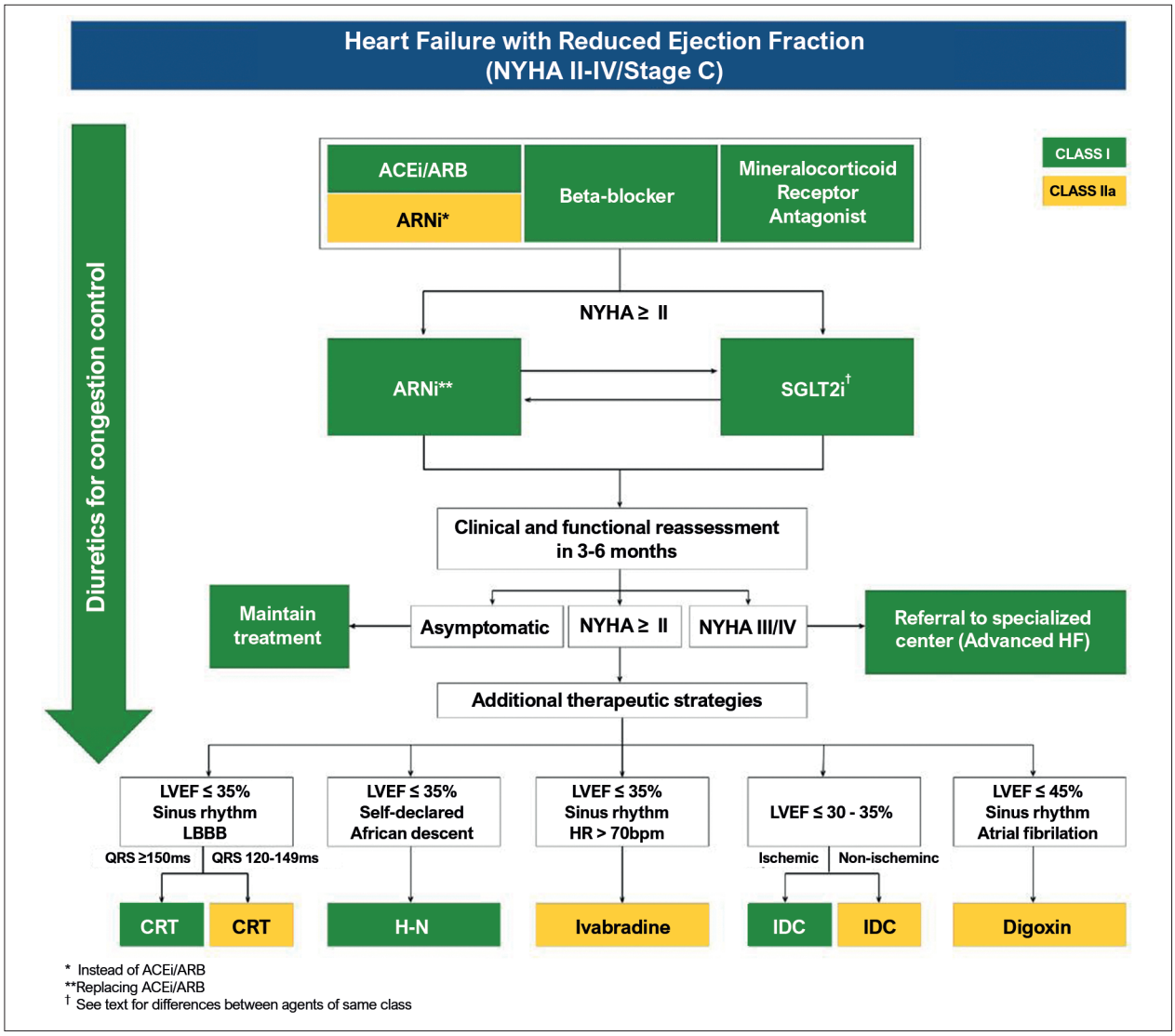


Figure 1 – *Treatment algorithm for heart failure with reduced ejection fraction. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; ARNI: angiotensin receptor-neprilysin inhibitor; CRT: cardiac resynchronization therapy; HF: heart failure; H-N: hydralazine-nitrate; HR: heart rate; ICD: implantable cardioverter-defibrillator; LBBB: left bundle branch block; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; SGLT2i: sodium-glucose cotransporter-2 inhibitor.2; NYHA: New York Heart Association; TRC: terapia de ressincronização cardíaca.*

Conclusion

The treatment of HFrEF can be laborious and require dedication of a multidisciplinary team to achieve the therapeutic goals of the guidelines, not always available to clinicians working alone in their offices. In this case, the introduction of multiple drugs at the same time may not be the ideal strategy.

Worryingly, there is still inertia in the adoption of recommended treatments, whether because of cost, fear of possible side effects, or ignorance regarding the benefit of therapeutic optimization.

Changing the HFrEF treatment sequence is nothing new and has been discussed in the past,[20] with a warning that there is no winner or loser in this fight against HFrEF.

Drugs that reduce morbidity and mortality in HFrEF should be prescribed using published guidelines as a source of knowledge dissemination and standardized continuing medical education. This will avoid confusion for physicians, risk of increased side effects, or use of doses lower than those indicated in guidelines.

In short, the most important task is to ensure access to all evidence-based therapies for all patients with HFrEF.

Author Contributions

Analysis and interpretation of the data and Writing of the manuscript: Rossi Neto JM; Critical revision of the manuscript for intellectual content: Rossi RM, Finger MA, Santos CC.

Potential Conflict of Interest

Dr. João Manoel Rossi Neto presented lectures for Novartis and Astra Zeneca. Dra. Carolina Casadei dos Santos presented lectures for Servier, Novartis, and Boehringer.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Januzzi JL Jr, Allen LA, Breathett K, Butler J, Davis LL, Fonarow GC, et al. 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure with Reduced Ejection Fraction: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2021;77(6):772-810. doi: 10.1016/j.jacc.2020.11.022.
2. Marcondes-Braga FG, Moura LAZ, Issa VS, Vieira JL, Rohde LE, Simões MV, et al. Emerging Topics Update of the Brazilian Heart Failure Guideline - 2021. Arq Bras Cardiol. 2021;116(6):1174-212. doi: 10.36660/abc.20210367.
3. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. Eur Heart J. 2021;42(36):3599-726. doi: 10.1093/eurheartj/ehab368.
4. Rohde LEP, Montera MW, Bocchi EA, Clausell NO, Albuquerque DC, Rassi S, et al. Diretriz Brasileira de Insuficiência Cardíaca Crônica e Aguda. Arq Bras Cardiol. 2018;111(3):436-539. doi: 10.5935/abc.20180190.
5. Greene SJ, Butler J, Hellkamp AS, Spertus JA, Vaduganathan M, DeVore AD, et al. Comparative Effectiveness of Dosing of Medical Therapy for Heart Failure: From the CHAMP-HF Registry. J Card Fail. 2021:S1071-9164(21)00393-6. doi: 10.1016/j.cardfail.2021.08.023.
6. Bhatt AS, Vaduganathan M, Claggett BL, Liu J, Packer M, Desai AS, et al. Effect of Sacubitril/Valsartan vs. Enalapril on Changes in Heart Failure Therapies Over Time: The PARADIGM-HF Trial. Eur J Heart Fail. 2021;23(9):1518-24. doi: 10.1002/ejhf.2259.
7. Kido K, Bianco C, Caccamo M, Fang W, Sokos G. Evaluating Sacubitril/Valsartan Dose Dependence on Clinical Outcomes in Patients with Heart Failure with Reduced Ejection Fraction. Ann Pharmacother. 2021;55(9):1069-75. doi: 10.1177/1060028020983522.
8. Paolillo S, Mapelli M, Bonomi A, Corrà U, Piepoli M, Veglia F, et al. Prognostic Role of β-blocker Selectivity and Dosage Regimens in Heart Failure Patients. Insights from the MECKI Score Database. Eur J Heart Fail. 2017;19(7):904-14. doi: 10.1002/ejhf.775.
9. Nauta JF, Santema BT, van der Wal MHL, Koops A, Warink-Riemersma J, van Dijk K, et al. Improvement in Left Ventricular Ejection Fraction After Pharmacological Up-titration in New-onset Heart Failure with Reduced Ejection Fraction. Neth Heart J. 2021;29(7-8):383-93. doi: 10.1007/s12471-021-01591-6.
10. Zoler ML. Experts Tout Immediate Quadruple Therapy for HFrEF Patients [Internet]. New York: Medscape. 2020 [cited 2021 Dec 7]. Available from: http://www.medscape.com/viewarticle/939465.
11. Greene SJ, Butler J, Fonarow GC. Simultaneous or Rapid Sequence Initiation of Quadruple Medical Therapy for Heart Failure-Optimizing Therapy With the Need for Speed. JAMA Cardiol. 2021;6(7):743-4. doi: 10.1001/jamacardio.2021.0496.
12. McMurray JJV, Packer M. How Should We Sequence the Treatments for Heart Failure and a Reduced Ejection Fraction?: A Redefinition of Evidence-Based Medicine. Circulation. 2021;143(9):875-7. doi: 10.1161/CIRCULATIONAHA.120.052926.
13. Packer M, McMurray JJV. Rapid Evidence-Based Sequencing of Foundational Drugs for Heart Failure and a Reduced Ejection Fraction. Eur J Heart Fail. 2021;23(6):882-94. doi: 10.1002/ejhf.2149.
14. Straw S, McGinlay M, Witte KK. Four Pillars of Heart Failure: Contemporary Pharmacological Therapy for Heart Failure with Reduced Ejection Fraction. Open Heart. 2021;8(1):e001585. doi: 10.1136/openhrt-2021-001585.
15. Fucili A, Cimaglia P, Severi P, Giannini F, Boccadoro A, Micillo M, et al. Looking for a Tailored Therapy for Heart Failure: Are We Capable of Treating the Patient Instead of the Disease? J Clin Med. 2021;10(19):4325. doi: 10.3390/jcm10194325.
16. Brownell NK, Ziaeian B, Fonarow GC. The Gap to Fill: Rationale for Rapid Initiation and Optimal Titration of Comprehensive Disease-modifying Medical Therapy for Heart Failure with Reduced Ejection Fraction. Card Fail Rev. 2021;7:e18. doi: 10.15420/cfr.2021.18.
17. Marschall A, Carnevali HC, Pascual CF, Rubio AL, Gallardo MJM, Bitriá CD, et al. Incidence and Predictors of Progression in Asymptomatic Patients with Stable Heart Failure. Am J Cardiol. 2021 Aug 1;152:88-93. doi: 10.1016/j.amjcard.2021.04.044.
18. Arvanitaki A, Michou E, Kalogeropoulos A, Karvounis H, Giannakoulas G. Mildly Symptomatic Heart Failure with Reduced Ejection Fraction: Diagnostic and Therapeutic Considerations. ESC Heart Fail. 2020;7(4):1477-87. doi: 10.1002/ehf2.12701.
19. Wood S. Four Pillars, Fast? Rapid Sequencing of HF Drugs Faces an Uphill Battle [Internet]. New York: TCTMD.com. 2021 [cited 2022 Jan 5]. Available from: https://www.tctmd.com/news/four-pillars-fast-rapid-sequencing-hf-drugs-faces-uphill-battle.
20. Willenheimer R, van Veldhuisen DJ, Silke B, Erdmann E, Follath F, Krum H, et al. Effect on Survival and Hospitalization of Initiating Treatment for Chronic Heart Failure with Bisoprolol Followed by Enalapril, as Compared with the Opposite Sequence: Results of the Randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III. Circulation. 2005;112(16):2426-35. doi: 10.1161/CIRCULATIONAHA.105.582320.

Rapid Sequencing of Foundational Treatment for HFrEF: The Innovative Proposal of John McMurray and Milton Packer

Bianca Lopes Cunha,[1] *Laura Leite da Escóssia Marinho,*[1] *Jefferson Luís Vieira*[1]
Hospital de Messejana Dr. Carlos Alberto Studart,[1] *Fortaleza, CE – Brazil*

The treatment of heart failure with reduced ejection fraction (HFrEF) involves implementing preventive measures, delaying disease progression, relieving symptoms and, above all, prolonging survival. The effectiveness of the drug arsenal for the management of HFrEF has been well established by several randomized clinical trials and is based on 4 foundational pillars of treatment: (1) β-blockers; (2) renin-angiotensin system inhibitors, including angiotensin-converting enzyme inhibitors (ACEis), angiotensin receptor blockers (ARBs), and angiotensin receptor-neprilysin inhibitors (ARNIs); (3) sodium-glucose cotransporter 2 inhibitors (SGLT2is); and (4) mineralocorticoid receptor antagonists (MRAs).

The conventional pharmacological approach presented by HFrEF treatment guidelines recommends sequential prescribing of the 4 foundational drug classes in the order in which they were tested in classic clinical trials.[1-4] Based on a 5-step protocol, physicians are instructed to initiate treatment with an ACEi/ARB, followed by a β-blocker and then an MRA. In step 4, replacement of the ACEi/ARB with an ARNI is considered and, finally, an SGLT2i can be added (Figure 1). This approach advises prescribers to titrate the dose of each drug to the target dose used in large-scale trials before initiating the next recommended drug class (Figure 2A). In 2021, however, a perspective article written by John McMurray and Milton Packer, authors of most of the main trials in the field in the last decade, pointed out a series of limitations in the conventional approach and proposed a new sequence of pharmacological treatment for ambulatory HFrEF based on 3 steps (Figure 2B).[5] According to the new proposal, the conventional approach presents an algorithm based on the historical order of publication of the clinical trials, wrongly assuming that the most effective and well-tolerated drugs were developed first. Another point observed by the authors is that the conventional approach prioritizes the achievement of the target dose of a given drug before initiating treatment with the next one, which can delay the achievement of optimal medical therapy by more than 6 months. Indeed, if we look at participants in large-scale clinical trials and surveys, we will see that a substantial percentage of them were not receiving recommended medications.[6,7] Even in recently completed trials, a meaningful proportion was not being treated with an MRA or an ARNI. In addition, proper sequencing of foundational drugs can improve safety and tolerability, as medications such as ARNIs can reduce the risk of renal insufficiency associated with ACEis/ARBs and both ARNIs and SGLT2is can mitigate the risk of hyperkalemia associated with the use of MRAs.

The new rapid sequencing strategy is based on the individual impact of each drug, even at low doses, with the goal of rapidly implementing the 4 medications within 4 weeks of initiating therapy. Step 1 recommends the simultaneous initiation of a β-blocker and an SGLT2i. β-blockers are the most effective drug class in the treatment of HFrEF, particularly at reducing all-cause mortality, while SGLT2is may reduce the risk of decompensation associated with the initiation of β-blocker therapy due in part to their early diuretic effect. Step 2 proposes the initiation of an ARNI within 1-2 weeks of Step 1, without the need to wait 2-4 weeks for the initiation of a new drug class as recommended by the conventional approach. The new strategy warns that, in patients with a systolic blood pressure <100 mm Hg, it may be prudent to try an ACEi or an ARB before initiation of an ARNI. Finally, 1-2 weeks later, Step 3 suggests the initiation of an MRA if potassium and renal function were favorable.

Despite the theoretical arguments presented for the adoption of this new therapeutic approach to HFrEF, practical barriers need to be discussed before this protocol can be implemented in clinical practice. First, the rapid sequencing approach has never been properly tested in a randomized clinical trial. Instead, the available evidence of benefit and safety favors the conventional approach, in which the addition of new drugs is studied in patients previously receiving standard care.8 The update of the Canadian Cardiovascular Society HF guidelines, for example, considers the use of rapid sequencing a reasonable alternative, but it recognizes that there is no robust evidence favoring one approach over the other.[9]

The clinical setting also plays a key role in the adoption of rapid sequencing. It is easier to initiate a series of new drugs in hospitalized patients assisted by a multidisciplinary team focused on quality of care than in outpatients. However, the authors of the new strategy recognize that rapid sequencing is safer and more appropriate for outpatients, and that caution is warranted in patients hospitalized for HF decompensation.

Finally, a practical barrier to rapid sequencing is the cost of initiating all 4 drugs at once, especially in populations that depend primarily on the public health system, as in Brazil.[10] In general, ACEis/ARBs, β-blockers and MRAs are usually cheaper and more accessible than new drugs such as ARNIs and SGLT2is. However, drug shortages in several health care units require frequent adjustments and replacements of patients' therapeutic regimens. It is not uncommon for the public sector, for example, to receive patients who have discontinued all medications a few months after

Keywords

Heart Failure; Adrenergic beta-Antagonists; Angiotensin-Converting Enzyme Inhibitors; Neprilysin; Mineralocorticoid Receptor Antagonists; Sodium-Glucose Transporter 2 Inhibitors

Mailing Address: Jefferson Luís Vieira •
Hospital de Messejana Dr. Carlos Alberto Studart Gomes – Av. Frei Cirilo, 3480. Postal Code 60.846-190, Messejana, Fortaleza, CE – Brazil
E-mail: jefvieira@yahoo.com.br
Manuscript received January 21, 2022, revised manuscript February 01, 2022, accepted February 16, 2022

DOI: https://doi.org/10.36660/abchf.20220005

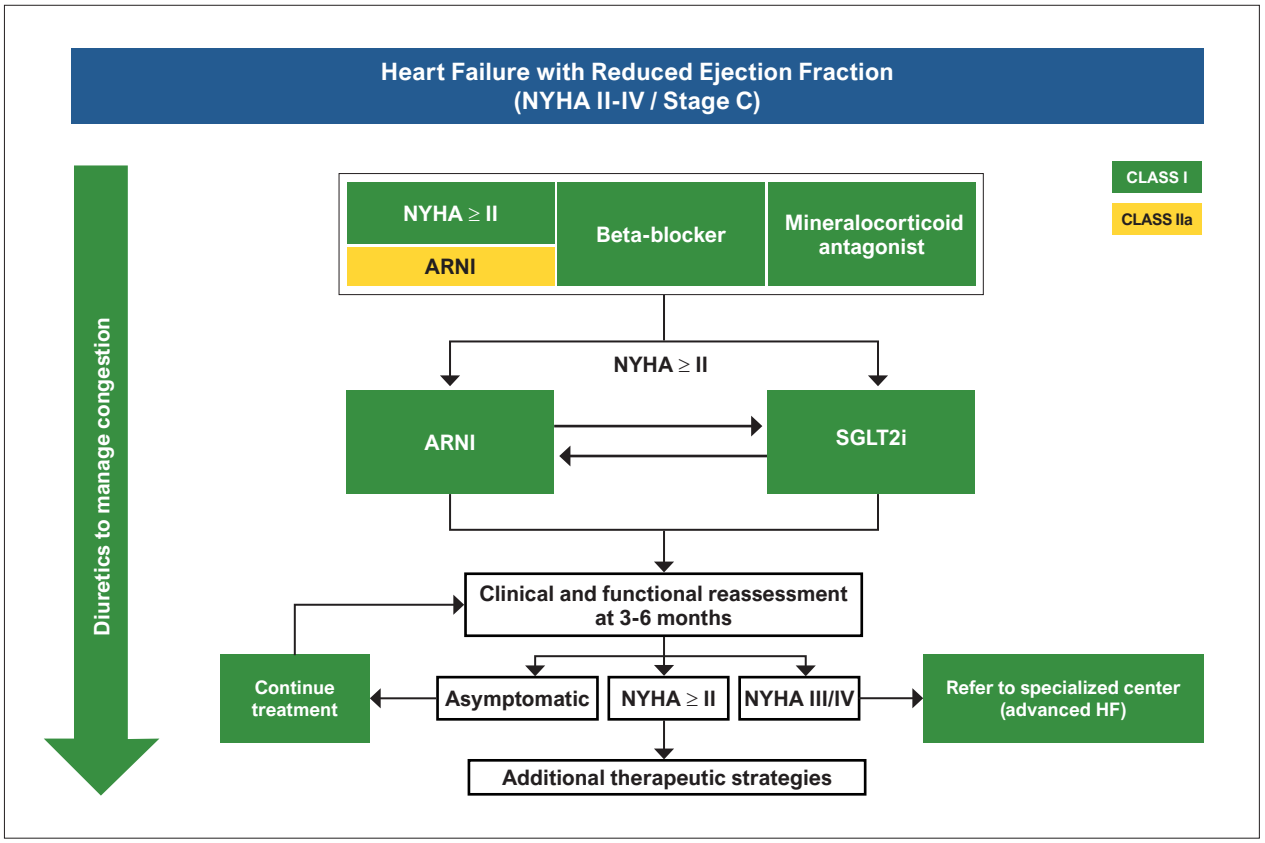


Figure 1 – *Algorithm for pharmacological treatment of heart failure with reduced ejection fraction adapted from the Brazilian Society of Cardiology. ARB: angiotensin receptor blocker; ACEi: angiotensin-converting enzyme inhibitor; ARNI: angiotensin receptor-neprilysin inhibitor; SGLT2i: sodium-glucose cotransporter 2 inhibitor; NYHA: New York Heart Association. Adapted from Marcondes-Braga FG, et al.*[2]

discharge because they cannot afford ARNIs/SGLT2is or because a certain cardioselective β-blocker is not available from the public health network in their hometown.

As a common point, these and other proposals for a pharmacological approach to HFrEF support that all patients with chronic HFrEF should be treated with all 4 foundational drugs, since each one acts on a specific pathophysiological pathway. Therefore, one of the main reasons for not using the treatment based on the "4 pillars" is related solely to therapeutic inertia. In the United States, it is estimated that less than 5%-10% of patients are receiving all 4 drugs, and the number of patients receiving these drugs at the target dose is even lower. Considering that each of the foundational drugs has proven to reduce HFrEF-related morbidity and mortality within 30 days of initiating treatment, every passing visit without the initiation of at least one additional drug could result in more hospitalizations and deaths, in addition to increasing tolerability to these medications. Therefore, more important than deciding whether the conventional or rapid sequencing approach should be used, we believe that there is an urgent need for strategies to increase medication prescribing according to current evidence, especially on an outpatient basis.

Author Contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data and Writing of the manuscript: Cunha BL, Vieira JL; Critical revision of the manuscript for intellectual content: Cunha BL, Marinho LLE, Vieira JL.

Potential Conflict of Interest

Dra. Laura Leite da Escóssia Marinho reports fees for serving as a speaker from Novartis. Dr. Jefferson Luís Vieira reports fees for serving on an adjudication committee from Academic Research Organization (ARO) at Hospital Israelita Albert Einstein and fees for serving as a speaker from Boehringer Ingelheim-Lilly and Novartis.

Sources of Funding

There were no external funding sources for this study.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Study Association

This article is part of the completion of medical residency by Bianca Lopes Cunha , from Hospital Messejana Dr. Carlos Alberto Studart.

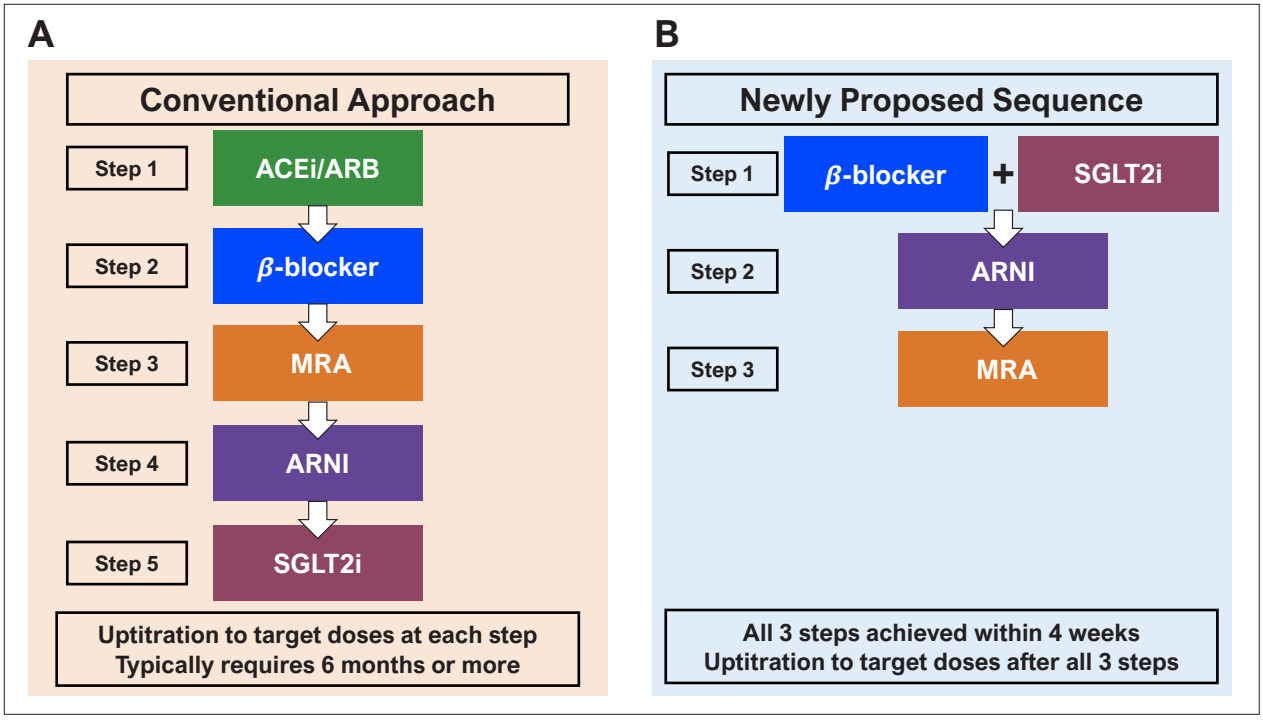


Figure 2 – *Conventional approach and rapid sequencing approach proposed by McMurray and Packer for the initiation of foundational drugs in outpatients with heart failure with reduced ejection fraction. MRA: mineralocorticoid receptor antagonist; ARB: angiotensin receptor blocker; ACEi: angiotensin-converting enzyme inhibitor; ARNI: angiotensin receptor-neprilysin inhibitor; SGLT2i: sodium-glucose cotransporter 2 inhibitor. Adapted from McMurray JJV, Packer M[5]*

References

1. Rohde LEP, Montera MW, Bocchi EA, Clausell NO, Albuquerque DC, Rassi S, et al. Diretriz Brasileira de Insuficiência Cardíaca Crônica e Aguda. Arq Bras Cardiol. 2018;111(3):436-539. doi: 10.5935/abc.20180190.
2. Marcondes-Braga FG, Moura LAZ, Issa VS, Vieira JL, Rohde LE, Simões MV, et al. Emerging Topics Update of the Brazilian Heart Failure Guideline - 2021. Arq Bras Cardiol. 2021;116(6):1174-212. doi: 10.36660/abc.20210367.
3. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. Eur Heart J. 2021;42(36):3599-726. doi: 10.1093/eurheartj/ehab368.
4. Maddox TM, Januzzi JL Jr, Allen LA, Breathett K, Butler J, Davis LL, et al. 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure with Reduced Ejection Fraction: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2021;77(6):772-810. doi: 10.1016/j.jacc.2020.11.022.
5. McMurray JJV, Packer M. How Should We Sequence the Treatments for Heart Failure and a Reduced Ejection Fraction?: A Redefinition of Evidence-Based Medicine. Circulation. 2021;143(9):875-7. doi: 10.1161/CIRCULATIONAHA.120.052926.
6. Greene SJ, Butler J, Albert NM, DeVore AD, Sharma PP, Duffy CI, et al. Medical Therapy for Heart Failure with Reduced Ejection Fraction: The CHAMP-HF Registry. J Am Coll Cardiol. 2018;72(4):351-66. doi: 10.1016/j.jacc.2018.04.070.
7. Albuquerque DC, Neto JD, Bacal F, Rohde LE, Bernardez-Pereira S, Berwanger O, et al. I Brazilian Registry of Heart Failure - Clinical Aspects, Care Quality and Hospitalization Outcomes. Arq Bras Cardiol. 2015;104(6):433-42. doi: 10.5935/abc.20150031.
8. Vaduganathan M, Claggett BL, Jhund PS, Cunningham JW, Ferreira JP, Zannad F, et al. Estimating Lifetime Benefits of Comprehensive Disease-modifying Pharmacological Therapies in Patients with Heart Failure with Reduced Ejection Fraction: A Comparative Analysis of Three Randomised Controlled Trials. Lancet. 2020;396(10244):121-8. doi: 10.1016/S0140-6736(20)30748-0.
9. McDonald M, Virani S, Chan M, Ducharme A, Ezekowitz JA, Giannetti N, et al. CCS/CHFS Heart Failure Guidelines Update: Defining a New Pharmacologic Standard of Care for Heart Failure With Reduced Ejection Fraction. Can J Cardiol. 2021;37(4):531-46. doi: 10.1016/j.cjca.2021.01.017.
10. Stevens B, Pezzullo L, Verdian L, Tomlinson J, George A, Bacal F. The Economic Burden of Heart Conditions in Brazil. Arq Bras Cardiol. 2018;111(1):29-36. doi: 10.5935/abc.20180104.

Viewpoint

Pharmacological Treatment Sequencing for Heart Failure with Reduced Ejection Fraction

Fabiana G. Marcondes-Braga[1]

Instituto do Coração (InCor), Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo,[1] São Paulo, SP – Brazil

Important advances in knowledge about the treatment of heart failure (HF) have been made over the past three decades.[1] In the 1980s, direct vasodilators, such as hydralazine and nitrate, and angiotensin-converting enzyme inhibitors (ACEis) were available. These drugs proved to be effective in the treatment of patients with different functional classes of HF. In CONSENSUS study, enalapril significantly reduced mortality, in patients with New York Heart Association (NYHA) class IV; number needed to treat - NNT, 6. as well as in patients with NYHA class II in SOLVD study, NNT 22.[2,3]

In the late 1990s, mineralocorticoid receptor antagonists and beta-blockers were revealed as two drug classes with an impact on mortality in patients with HF with reduced ejection fraction (HFrEF). In RALES study, spironolactone significantly reduced mortality in patients with NYHA class III-IV NNT 10, leading to early study discontinuation.[4] Beta-blockers, in turn, changed the natural history of HFrEF, as three different drugs (carvedilol, metoprolol succinate, and bisoprolol) reduced the relative risk of overall death by approximately 35% compared to placebo.[5-7]

In the 2000s, several studies evaluated the effects of implantable devices such as implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy (CRT), in patients with HFrEF, showing reduction in mortality rate and improvement in quality of life. The benefits of ICD were remarkable especially in patients with ischemic cardiomyopathy, while CRT mainly benefited patients with left ventricular ejection fraction (LVEF) ≤ 35%, wide QRS (> 150 ms), and left bundle branch block morphology.[8]

In 2010, ivabradine, a new class of drug for the treatment of HFrEF was described. This drug acts on the sinus node, reducing heart rate (HR), and has been shown to significantly reduce hospitalizations and cardiovascular death in patients in sinus rhythm with LVEF lower or equal to 35% and HR higher or equal to 70 bpm.[9]

Keywords

Heart failure with reduced ejection fraction; Drug Therapy.

Mailing Address:: Fabiana G. Marcondes-Braga •
Núcleo de Transplante Cardíaco do InCor – Av. Dr. Enéas de Carvalho Aguiar, 44, Bloco 1, 2º Andar. CEP 05403-000, São Paulo, SP – Brazil
E-mail: fgmarcondes@yahoo.com.br, fgmarcondes@gmail.com
Manuscript received January 24, 2022, revised manuscript February 01, 2022, accepted February 16, 2022

DOI: https://doi.org/10.36660/abchf.20220006

In 2014, sacubitril/valsartan, a new class of drug comprising an angiotensin receptor-neprilysin inhibitor (ARNi) plus an angiotensin receptor blocker (ARB), was tested against enalapril in patients with HFrEF. A 20% reduction in cardiovascular death or hospitalization for HF was identified (NNT 21). Also, a 20% reduction in cardiovascular death as a single outcome. In subsequent analyses, sacubitril/valsartan also showed sudden death rate reduction, especially in patients with NYHA II HFrEF.[10]

More recently, studies involving diabetic patients have revealed that sodium-glucose cotransporter 2 inhibitors (SGLT2i) are able to reduce major cardiovascular events and hospitalizations for HF. Subsequent studies have shown that dapagliflozin (DAPA-HF study)[11] and empagliflozin (EMPEROR-Reduced study)[12] significantly reduce cardiovascular death and hospitalization for HF (25% relative risk reduction) in patients with HFrEF (LVEF < 40%), regardless the presence of diabetes. Patients in both studies were on guideline directed medical therapy (GDMT): approximately 95% on beta-blocker, 90-97% on ACEi/ARB/ ARNi, and 70% on mineralocorticoid receptor antagonist).

Two other drug classes have also been tested recently. Vericiguat, a soluble guanylate cyclase stimulator, has been shown to reduce cardiovascular death and hospitalization for HF in patients NYHA class II/III reporting recent hospitalization, while omecamtiv mercabil, a selective cardiac myosin activator, has reduced the primary outcome in GALACTIC study. However, none of these drugs has been approved for use in Brazil yet.[13] Finally, intravenous iron was shown to reduce hospitalizations for HF in patients hospitalized for decompensated HF in the AFFIRM-HF study, . No impact on mortality was observed.[14]

Figure 1 illustrates this historical sequence and major studies that have revealed the effects of these drugs on HFrEF patients.

Recently, an analysis comparing conventional therapy (ACEi and beta-blocker) with comprehensive therapy (ARNi/beta-blocker/mineralocorticoid receptor antagonist/SGLT2i), involving data from three large HFrEF studies (15,880 patients), has concluded that comprehensive therapy can provide 6.3 additional years of life. Even by adding a mineralocorticoid receptor antagonist to conventional therapy, comprehensive therapy can provide up to 3.1 additional years of life to the population with HFrEF.[15]

In view of the new evidence, SGLT2is were considered first-line therapy to reduce mortality in HFrEF together with the established therapies, which act on the renin-angiotensin-aldosterone system and the sympathetic nervous system.[16] Given that all drug classes mentioned herein have an early effect on mortality – as of 14 days in the SOLVD study (enalapril), 28 days in the COPERNICUS study (carvedilol),

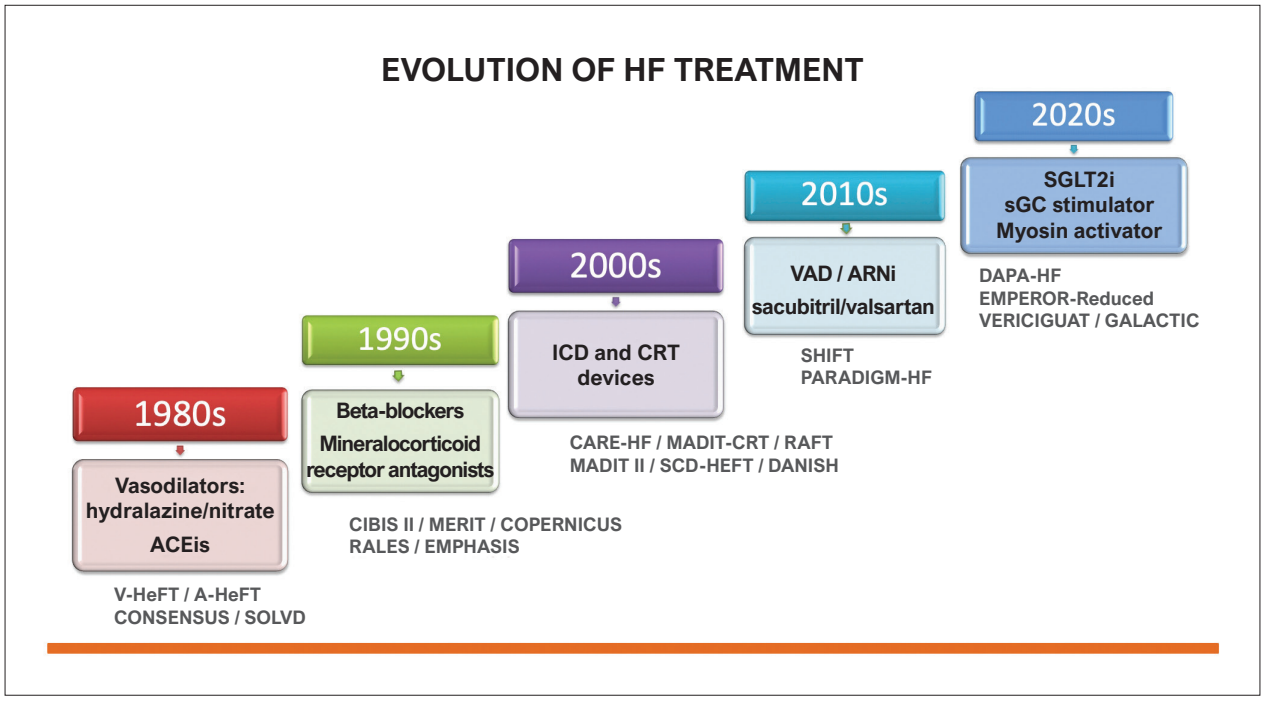


Figure 1 – *Evolution of the treatment of heart failure (HF) with reduced ejection fraction. ACEi: angiotensin-converting enzyme inhibitor; ICD: implantable cardioverter-defibrillator; CRT: cardiac resynchronization therapy; VAD: long-term ventricular assist device; ARNi: angiotensin receptor-neprilysin inhibitor; SGLT2i: sodium-glucose cotransporter 2 inhibitor; sGC: soluble guanylate cyclase.*

30 days in the EPHESUS study (eplerenone), 30 days in the PARADIGM study (sacubitril/valsartan), 28 days in the DAPA-HF study (dapagliflozin), and 28 days in the EMPEROR-Reduced study (empagliflozin)[17] –, early use of quadruple therapy is now recommended by different societies.[13,18,19] Thus, contemporary treatment of HFrEF involves the early use of therapies that are proven to reduce mortality in optimized doses.

Cardiac societies have updated their guidelines over the past 2 years and were unanimous in considering the drugs that reduce mortality in HFrEF as first-line therapy with a class I recommendation.

The US society guideline suggests starting beta-blockers and ACEi/ARB/ARNi, emphasizing a preference for ARNi, then adding mineralocorticoid receptor antagonist and SGLT2i if NYHA class II-IV. The European society guideline does not determine the sequence of therapies but establishes that the four drugs should be started early (ARNi/ACEi + beta-blocker + mineralocorticoid receptor antagonist + SGLT2i). According to the Brazilian Society of Cardiology heart failure guideline, the use of drugs with impact on mortality is also considered class I recomendation. It reinforces the importance of combining SGLT2i with triple therapy and replacing ACEi with ARNi in NYHA class II patients early. It is also highlighted that symptomatic patients deserve to receive therapy with 4 drugs in optimized doses as soon as possible. The concept of waiting 3-6 months with triple therapy to add or substitute one of them has been considered outdated. Starting treatment with ARNi instead of ACEi is also discussed in the document. This proposal is considered a class IIa recommendation because it is based on studies with surrogate instead of hard outcomes (PARADIGM study).

Thus, although there are slight differences between the guidelines regarding the initial approach to patients with HFrEF, they all highlight the importance of using four different classes of drug at optimized doses as early as possible, as shown in Figure 2.

However, considering that the new drugs were not evaluated incrementally and there is no direct comparison between them, the most appropriate sequencing is yet to be established. Therefore, clinical cardiologists must define how and in which sequence to use the new therapies for HF.[20]

Based on this gap, different groups have proposed different strategies for sequencing therapies for HF. The conventional strategy follows a historical sequence in which drugs are introduced according to the temporal discovery of the benefits of each therapy in HF: start with ACEi, add beta-blocker and mineralocorticoid receptor antagonist, replace ACEi with ARNi if symptomatic, and, finally, add SGLT2i. In this strategy, each added therapy must be optimized to the maximum dose before initiating subsequent therapy.

Recently, professors John McMurray and Milton Packer have proposed a rapid three-step sequencing in which initial treatment includes beta-blocker and SGLT2i, followed by ARNi and mineralocorticoid receptor antagonist. One of their reasons for choosing this sequence is the early reduction in mortality caused by all drugs. Therefore, the faster they are started, the greater the benefit, which occurs regardless of previous therapies.[17] The authors venture a proposal of optimization within 4

weeks, which may be quite challenging considering that patients with HF tend to be more hypotensive, present with renal dysfunction, and develop volume oscillations, which must be managed with caution.

Thus, the most appropriated strategy for the initial management of HFrEF patients is the personalized treatment, focusing on the use of quadruple therapy as early as possible.

In my point of view, pharmacologycal treatment sequencing may be guided by HFrEF patients profile. Patients with HFrEF may present with different clinical profiles that include hypertension, hypotension, congestion, renal dysfunction, hyperkalemia, and diabetes, among others. Figure 3 shows a proposal for the initial management of patients with HFrEF considering these different profiles

In sum, the current first-line HF treatment includes four different drugs that have an important impact on mortality reduction. Tailored treatment seems to be the best strategy for the initial management of these patients.

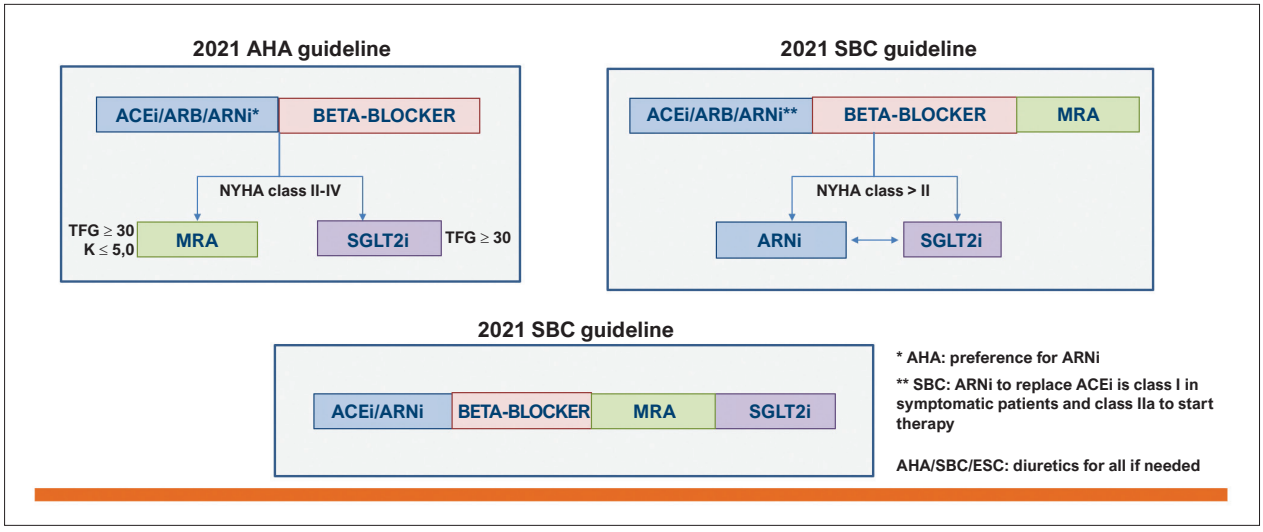


Figure 2 – *Use of first-line treatment of HFrEF according to different guidelines. AHA: American Heart Association; SBC: Brazilian Society of Cardiology; ESC: European Society of Cardiology; ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; ALDO ANT: aldosterone antagonist; SGLT2i: sodium-glucose cotransporter 2 inhibitor; ARNi: angiotensin receptor-neprilysin inhibitor; NYHA: New York Heart Association; GFR: glomerular filtration rate; K: potassium.*

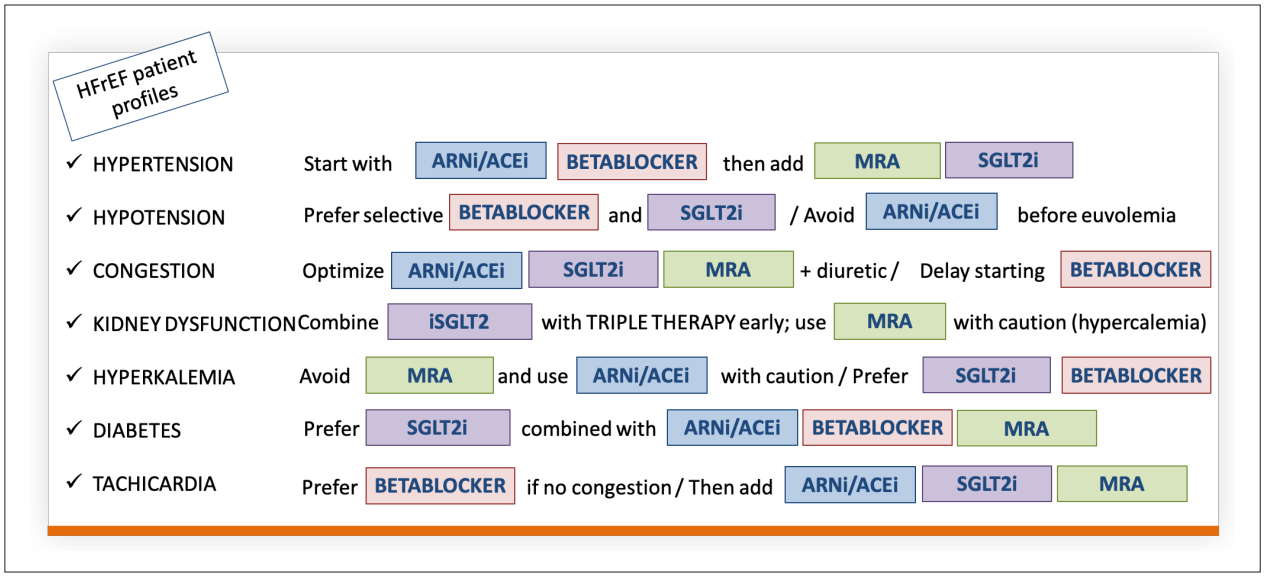


Figure 3 – *A proposal of clinical management of patients with HFrEF according to individual characteristics. HFrEF: heart failure with reduced ejection fraction; ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; MRA: mineralocorticoid receptor antagonist; SGLT2i: sodium-glucose cotransporter 2 inhibitor; ARNi: angiotensin receptor-neprilysin inhibitor.*

Author Contributions

Conception and design of the research; Acquisition of data; Analysis and interpretation of the data; Statistical analysis; Obtaining financing; Writing of the manuscript and Critical revision of the manuscript for intellectual contente: Marcondes-Braga FG.

Potential Conflict of Interest

Dra. Fabiana G. Marcondes-Braga: Advisory Board and speaker: Novartis; Astra Zeneca; Boehringher; Bayer.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Marcondes-Braga FG, Ramires FJA, Figueiredo EL, Figueiredo Neto JA, Beck-da-Silva L, Rassi S. Emerging Topics in Heart Failure: New Era of Pharmacological Treatment. Arq Bras Cardiol. 2020;115(5):956-60. doi: 10.36660/abc.20201106.
2. CONSENSUS Trial Study Group. Effects of Enalapril on Mortality in Severe Congestive Heart Failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med. 1987;316(23):1429-35. doi: 10.1056/NEJM198706043162301.
3. Yusuf S, Pitt B, Davis CE, Hood WB Jr, Cohn JN. Effect of Enalapril on Mortality and the Development of Heart Failure in Asymptomatic Patients with Reduced left Ventricular Ejection Fractions. N Engl J Med. 1992;327(10):685-91. doi: 10.1056/NEJM199209033271003.
4. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999;341(10):709-17. doi: 10.1056/NEJM199909023411001.
5. Effect of Metoprolol CR/XL in Chronic Heart Failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet. 1999;353(9169):2001-7.
6. Packer M, Fowler MB, Roecker EB, Coats AJ, Katus HA, Krum H, et al. Effect of Carvedilol on the Morbidity of Patients with Severe Chronic Heart Failure: Results of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study. Circulation. 2002;106(17):2194-9. doi: 10.1161/01.cir.0000035653.72855.bf.
7. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): A Randomised Trial. Lancet. 1999;353(9146):9-13.
8. Rohde LEP, Montera MW, Bocchi EA, Clausell NO, Albuquerque DC, Rassi S, et al. Diretriz Brasileira de Insuficiência Cardíaca Crônica e Aguda. Arq Bras Cardiol. 2018;111(3):436-539. doi: 10.5935/abc.20180190.
9. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, et al. Ivabradine and Outcomes in Chronic Heart Failure (SHIFT): A Randomised Placebo-controlled Study. Lancet. 2010;376(9744):875-85. doi: 10.1016/S0140-6736(10)61198-1.
10. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin Inhibition Versus Enalapril in Heart Failure. N Engl J Med. 2014;371(11):993-1004. doi: 10.1056/NEJMoa1409077.
11. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019;381(21):1995-2008. doi: 10.1056/NEJMoa1911303.
12. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. 2020;383(15):1413-24. doi: 10.1056/NEJMoa2022190.
13. Marcondes-Braga FG, Moura LAZ, Issa VS, Vieira JL, Rohde LE, Simões MV, et al. Emerging Topics Update of the Brazilian Heart Failure Guideline - 2021. Arq Bras Cardiol. 2021;116(6):1174-212. doi: 10.36660/abc.20210367.
14. Ponikowski P, Kirwan BA, Anker SD, McDonagh T, Dorobantu M, Drozdz J, et al. Ferric Carboxymaltose for Iron Deficiency at Discharge After Acute Heart Failure: a Multicentre, Double-blind, Randomised, Controlled Trial. Lancet. 2020;396(10266):1895-904. doi: 10.1016/S0140-6736(20)32339-4.
15. Vaduganathan M, Claggett BL, Jhund PS, Cunningham JW, Ferreira JP, Zannad F, et al. Estimating Lifetime Benefits of Comprehensive Disease-modifying Pharmacological Therapies in Patients with Heart Failure with Reduced Ejection Fraction: A Comparative Analysis of Three Randomised Controlled Trials. Lancet. 2020;396(10244):121-8. doi: 10.1016/S0140-6736(20)30748-0.
16. Bhatt DL, Verma S, Braunwald E. The DAPA-HF Trial: A Momentous Victory in the War against Heart Failure. Cell Metab. 2019;30(5):847-9. doi: 10.1016/j.cmet.2019.10.008.
17. Packer M, McMurray JJV. Rapid Evidence-based Sequencing of Foundational Drugs for Heart Failure and a Reduced Ejection Fraction. Eur J Heart Fail. 2021;23(6):882-894. doi: 10.1002/ejhf.2149.
18. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021 Sep 21;42(36):3599-3726. doi: 10.1093/eurheartj/ehab368.
19. Maddox TM, Januzzi JL Jr, Allen LA, Breathett K, Butler J, Davis LL, et al. 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure with Reduced Ejection Fraction: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2021;77(6):772-810. doi: 10.1016/j.jacc.2020.11.022.
20. Bhatt AS, Abraham WT, Lindenfeld J, Bristow M, Carson PE, Felker GM, et al. Treatment of HF in an Era of Multiple Therapies: Statement From the HF Collaboratory. JACC Heart Fail. 2021;9(1):1-12. doi: 10.1016/j.jchf.2020.10.014.

Sequencing of Pharmacotherapy for Heart Failure with Reduced Ejection Fraction: A Clinical Profile-Based Approach

Luís Beck-da-Silva[1,2]

Departamento de Medicina Interna da Universidade Federal do Rio Grande do Sul (UFRGS),[1] *Porto Alegre, RS – Brazil*
Serviço de Cardiologia do Hospital de Clínicas de Porto Alegre (HCPA),[2] *Porto Alegre, RS – Brazil*

A Brief History of Heart Failure (HF) Treatment

Until 1987, HF treatment consisted in:

– Recommendation of a low-sodium diet;

– Diuretics for manifestations of congestion;

– Digoxin;

– Rest.

None of these recommendations was based on clinical or epidemiological evidence, instead relying on the pathophysiological knowledge of the disease at the time, the pharmacological effect of medications, and good sense.

In 1987, a new era of HF treatment began with the publication of the first large randomized clinical trial that tested a drug that could inhibit a hormonal axis involved in causing, maintaining, and increasing risk for this disease. This axis was the renin-angiotensin-aldosterone system (RAAS), and this drug was enalapril.[1] At that moment, the addition of a drug to the clinical treatment of patients with HF could reduce relative risk of death by 50%.

Subsequently, the history of HF treatment would change consistently. If inhibiting the RAAS generated such a significant and relevant response, the inhibition of the adrenergic system (knowingly activated in patients with HF) would be the next hypothesis to be tested. At that time, medical textbooks contraindicated the use of adrenergic blockers in patients with HF, since the rationale was that these would worsen ventricular performance and patients' clinical picture. Scandinavian researchers pursued the hypothesis that an adrenergic blockade would be beneficial, and we all know the outcome of this chapter of HF treatment history. Multicenter randomized clinical trials ensued, testing ß-blockers in patients with HF and discovering the second drug class capable of changing the natural history of this disease.[2-4]

In the last decades, there was significant progress in the pathophysiological understanding of HF and in the awareness of the utility of the inhibition of counterregulatory hormones with damaging effects in the disease. Additional inhibition of the RAAS was the new hypothesis after the confirmation of ß-blockers.[5] Low-dose spironolactone, more through its hormonal effect than its diuretic effect, was the next drug to be proven beneficial to the prognosis of HF.[6]

After the publication of RALES[6] and the quick implementation of this knowledge on clinical practice, we went through a period of almost 20 years of apparent stagnation in the pharmacological treatment of HF. The most relevant innovations in this period either did not present an isolated effect on mortality[7] or provided benefits to specific subgroups only.[8]

For 2 decades, the basic treatment of patients with HF consisted in an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB), a ß-blocker, and spironolactone.

A new era in HF treatment

A new, modern era in HF treatment begins with the arrival of new drugs with prognostic effects in the prognostic of patients with HF.

– Angiotensin receptor-neprilysin inhibitors (ARNI).

Unequivocal evidence has been established by at least 2 large-scale studies with enalapril, which showed that interfering with the renin-angiotensin system reduces mortality in patients with HF and reduced ejection fraction.[1,9] This approach was reinforced by studies with ACEI and ARB in patients with HF and/or left ventricular systolic dysfunction after acute myocardial infarction.[10,11]

Subsequently, the new hypothesis considered for HF treatment was inhibiting the degradation of natriuretic peptides (BNP) and other vasoactive peptides with potentially "compensatory" effects through neprilysin inhibition and observing the clinical effect. By inhibiting BNP degradation, the increase in circulating BNP results in more vasodilation and natriuresis mediated by endogenous BNP. The PARADIGM-HF study tested a neprilysin inhibitor called sacubitril in association with valsartan, a known ARB, in direct comparison with enalapril in the treatment of patients with HF. This large multicenter, randomized clinical trial with over 7000 patients established the superiority of sacubitril/valsartan over enalapril, thus cementing the importance of the simultaneous inhibition of neprilysin and the RAAS.[12] When compared to enalapril, the relative risk reduction with sacubitril/valsartan was 20% for cardiovascular mortality and 20% for hospitalizations

Keywords

Sodium-Glucose Transporter 2 Inhibitors; Adrenergic beta-Antagonists; Mineralocorticoid Receptor Antagonists.

Mailing Address: Luís Beck-da-Silva •
Serviço de Cardiologia, Hospital de Clínicas de Porto Alegre (HCPA) - Rua Ramiro Barcelos, 2350. Postal Code 90035-003, Porto Alegre, RS - Brazil
E-mail: lbneto@hcpa.edu.br, luisbeckdasilva@gmail.com
Manuscript received February 01, 2022, revised manuscript February 14, 2022, accepted February 14, 2022

DOI: https://doi.org/10.36660/abchf.20220007

due to HF; both effects were demonstrated at statistically significant evidence levels ($p < 0.00001$). When performing a putative comparison with placebo, the estimated benefits of sacubitril/valsartan were a 30–35% reduction in cardiovascular death and a 45–50% reduction in hospitalizations for HF.[13]

– Sodium–glucose co-transporter 2 inhibitors (SGLT2i).

This innovative drug class, initially tested as antidiabetic drugs,[14] became a recent innovation in the pharmacological treatment of HF.

Two studies (DAPA-HF and EMPEROR-Reduced) demonstrated a 30% reduction in the risk of hospitalization for HF when patients were treated with dapagliflozin or empagliflozin when compared to placebo.[15,16] The benefit of these drugs was observed both in patients with diabetes and HF and those without diabetes but with a similar degree of HF.

Moreover, SGLT2i were demonstrated to reduce the risk of cardiovascular death or total mortality in clinical trials with patients with chronic HF, type 2 diabetes, and chronic kidney disease.[15-17]

After the publication of these pivotal studies, the benefits of SGLT2i to survival were supported by a meta-analysis of studies with patients with HF and reduced ejection fraction, as well as a meta-analysis of studies with patients with diabetes.[18,19]

With this evidence, SGLT2i became the fourth pillar of the clinical treatment of HF, together with ACEI/ARNI, ß-blockers, and spironolactone.

Sequencing of HF Treatment

With the emergence of 5 drug classes, distributed on 4 main pillars, with consistent effects on the increase in patient survival, the concept of sequencing was created. Based on expert opinions and comparative analyses of clinical trials, here we discuss "how to make" an increasingly more complex prescription.

Option 1: historical sequencing

Historical sequencing aims to reproduce, in the patient's prescription, the historical order in which medications were studied. It thus begins with an ACEI, followed by ß-blockers and spironolactone. Subsequently, the ACEI would be swapped by an ARNI, and an SGLT2i would be added to the prescription.

In this option,

✓ each drug dose is increased to its maximum before moving on to the next drug class;

✓ many visits are required;

✓ reaching optimal treatment may take 6 or more months;

✓ the benefit is delayed.

An argument against this sequencing method is that foundational drugs already reduce mortality in small initial doses, in an independent manner, and a significant beneficial effect is observed in less than 30 days. Therefore, delaying the start of a new therapeutic class would not be justified.[20] Figure 1.

Option 2: Packer and McMurray sequencing

The sequencing strategy recently proposed by Milton Packer and John McMurray[20] proposes that HF treatment be initiated with a ß-blocker and an SGLT2i. Subsequently, an ARNI or spironolactone would be added to the prescription. In case of hypotension, the ARNI would be postponed; in case of hyperkalemia, spironolactone should be postponed. Figure 2.

The reasons given by the authors are based in part on pathophysiological reasoning, where the adrenergic system is the first to be activated in the neurohormonal cascade of HF and thus should be the first to be inhibited; and in part on clinical and epidemiological reasoning based on clear evidence of prevention of sudden death by ß-blockers. The authors recognize the need to achieve clinical euvolemia for the safe start of ß-blockers and argue that the concomitant start of SGLT2i, a drug class that affects the SGLT2 in the proximal tubule of the nephron (thus having a diuretic effect), would compensate for the risk of worsening congestion attributable to ß-blockers.

The arguments of caution regarding the Packer e McMurray sequencing method are basically the following:

✓ many patients, especially treatment-naïve ones, are initially congested, thus not being candidates for the use of ß-blockers as initial drugs;

✓ Most of them will require diuretics to reach the desired euvolemia, since the diuretic effect of SGLT2i is, at best, discrete;

✓ In this time window while we cannot start a ß-blocker, why not initiate treatment with a vasodilator (ARNI or ACEI) to offer this immediate benefit to patients? The Packer and McMurray sequencing method does not contemplate this frequent clinical scenario;

✓ From a clinical and epidemiological standpoint, the hypothesis of using a ß-blocker as the initial approach in the pharmacological treatment of HF was specifically tested by CIBIS III. This clinical trial compared an approach that started therapy with enalapril (ACEI) to one that started therapy with bisoprolol (ß-blocker). In this trial, although the result was neutral, therapy starting with a ß-blocker presented an increase (RR = 1.25) in hospitalizations for HF (not statistically significant).

Therefore, starting with a ß-blocker was not a superior strategy and showed a trend of increase in hospitalizations.

Considering these favorable and unfavorable aspects of a fixed suggestion of drug sequencing when initiating clinical treatment of HF, it is important to note that the authors themselves postulated that "safety and tolerance improve with appropriate class sequencing".[20] With this aim, we seek to describe what would be an appropriate sequencing of drug classes, which would certainly adapt its priorities to the patient's clinical profile.

Option 3: sequencing based on clinical profiles

The start and sequencing of foundational drugs for the appropriate treatment of patients with HF should follow some basic premises that are highly grounded in epidemiological and clinical evidence. These are:

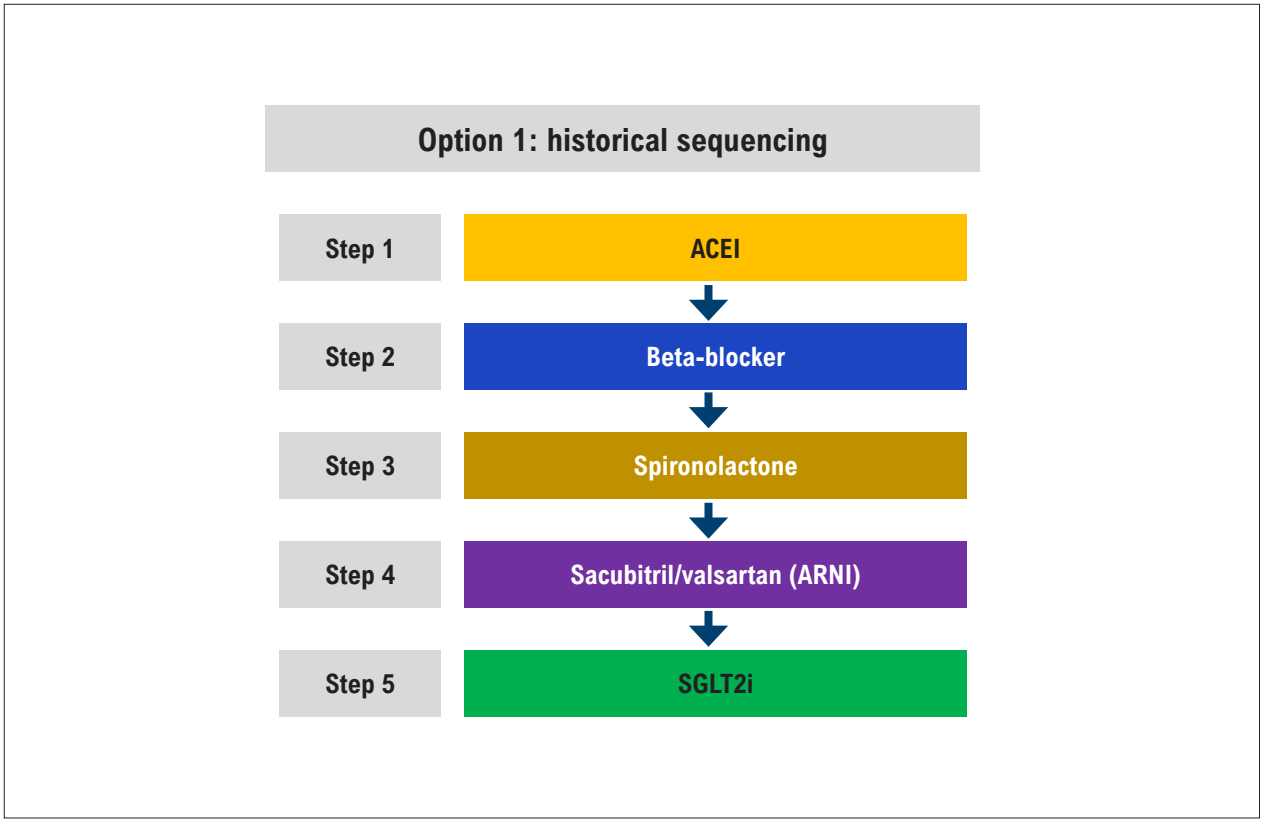


Figure 1 – *Historical sequencing of HF treatment. ACEI: angiotensin-converting enzyme inhibitor; SGLT2i: sodium–glucose co-transporter 2 inhibitor.*

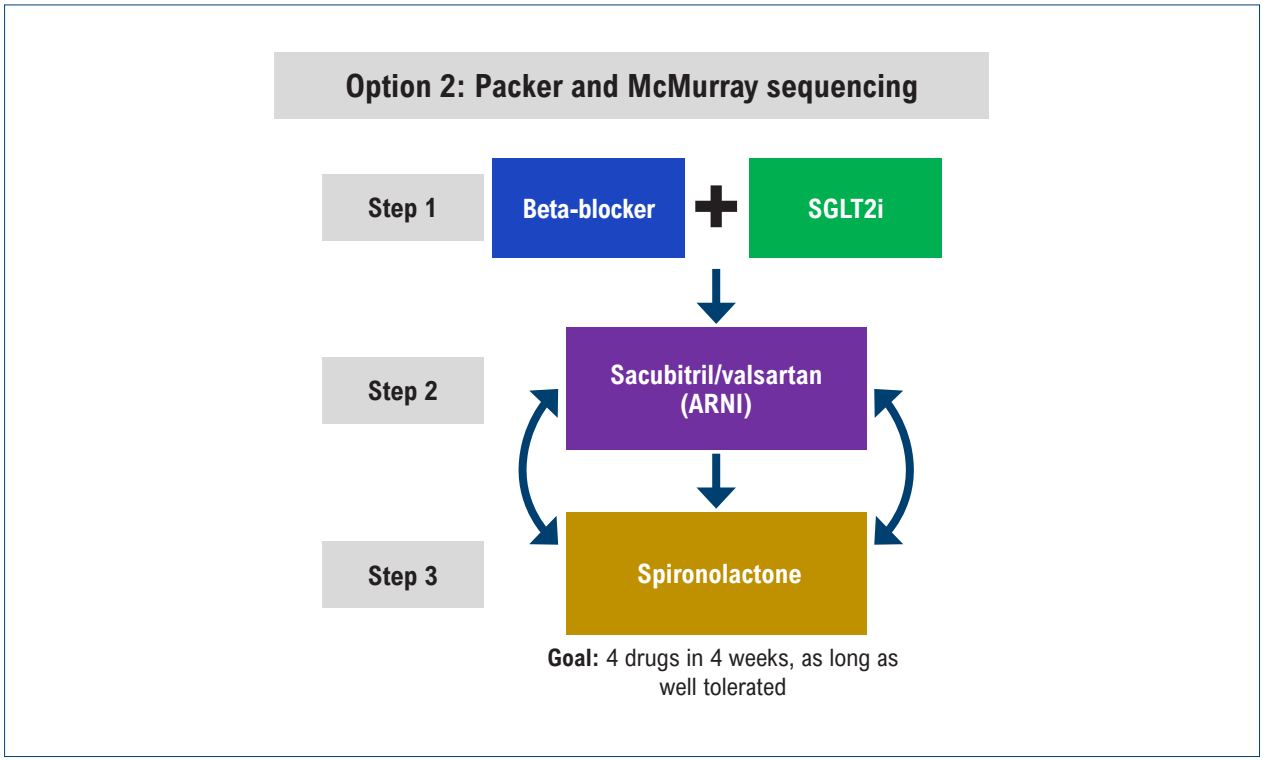


Figure 2 – *Sequencing of HF treatment according to Packer and McMurray. *Adapted from M. Packer and J.J.V. McMurray. European Journal of Heart Failure (2021).[20] ARNI: Angiotensin receptor-neprilysin inhibitors.*

1. Five drug classes must occupy the 4 foundational pillars of HF treatment: a. ACEI or ARNI; b. ß-blocker; c. spironolactone; d. SGLT2i;

2. The magnitude of the benefit provided by each drug class does not depend on treatment with other classes. A modern example of this evidence is the fact that, among patients in the DAPA-HF[15] and EMPEROR Reduced studies,[16] the subgroups who used ARNI or not had similar benefits (for a composite outcome of cardiovascular death or hospitalization for HF: RR = 0.68 [95%CI 0.53–0.89] with ARNI and RR = 0.75 [95%CI 0.68–0.84] without ARNI);

3. The foundational drugs reduce morbidity and mortality already in their low initial doses.[21] Benefits are relevant and noticeable within the first 30 days. An example is the great separation of survival curves in the COPERNICUS study, noticeable at 4 weeks, with a mean dose of 6.5 mg twice a day;[22]

4. The addition of a new drug class provides greater benefit than an increase in dose of an already employed drug.[20]

Considering these fundamental premises, we believe that the same result cannot be obtained by using the same drug sequence in all patients. Therefore, Figure 3 expresses the choices made by this author for prioritizing drugs based on patients' clinical profiles.

Take-home messages

✓ The pharmacological treatment of HF is based on 4 pillars according to the prognostic effect of drugs considered foundational.

✓ Efforts must be made to prioritize the benefit of all drugs with the concept that "a little of each drug is better than a lot of fewer drugs."

✓ It is recommended that all 4 classes of foundational drugs be initiated in the short-term (4–6 weeks).

✓ We advise that the start and sequencing of HF treatment be done by respecting the clinical profile of each patient in order to increase tolerance, safety, and therapeutic success.

Author Contributions

Conception and design of the research, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Beck-da-Silva L.

Potential Conflict of Interest

Participated in Board Meetings of Astra-Zeneca, Boehringer Ingelheim, Novartis. Speaker for Novartis, Boehringer Ingelheim, Pfizer and Viphor. Research support from Novartis, Boehringer Ingelheim, IONIS and AMGEN.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

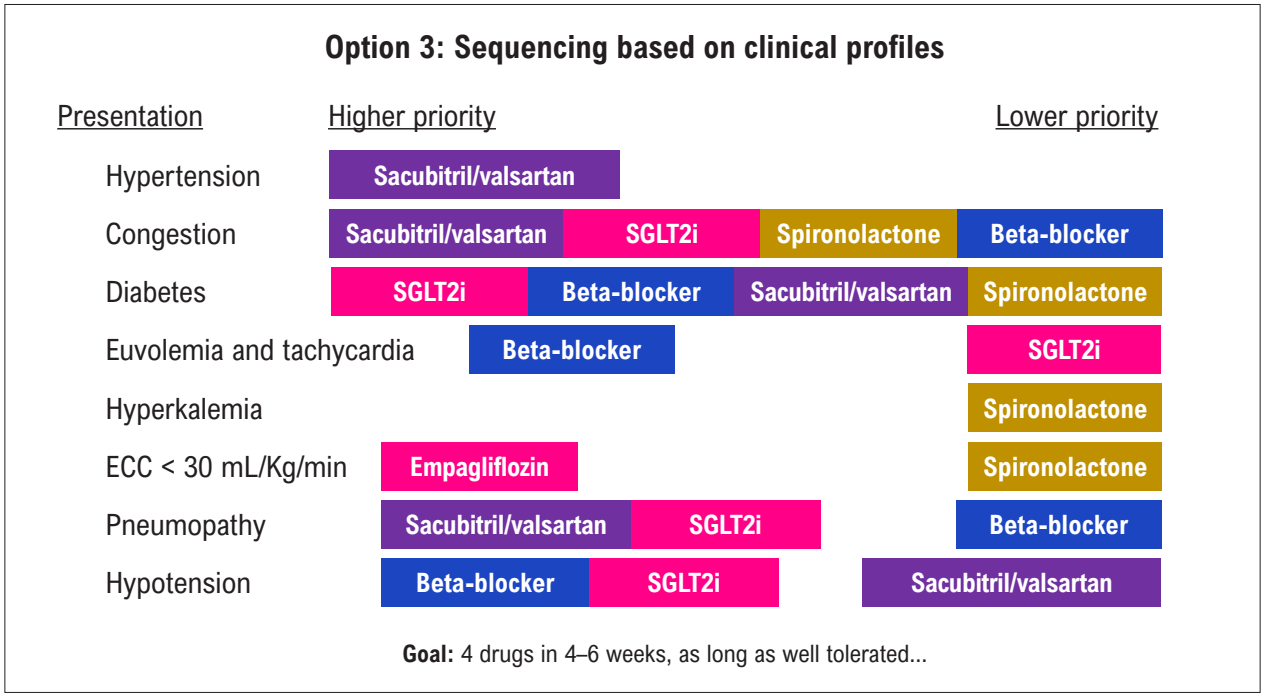


Figure 3 – *Sequencing of HF treatment based on clinical profiles. SGLT2i: sodium–glucose co-transporter 2 inhibitors; ECC: endogenous creatinine clearance.*

References

1. CONSENSUS Trial Study Group. Effects of Enalapril on Mortality in Severe Congestive Heart Failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med. 1987;316(23):1429-35. doi: 10.1056/NEJM198706043162301.
2. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, et al. The Effect of Carvedilol on Morbidity and Mortality in Patients with Chronic Heart Failure. U.S. Carvedilol Heart Failure Study Group. N Engl J Med. 1996;334(21):1349-55. doi: 10.1056/NEJM199605233342101.
3. CIBIS-II Investigators Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet. 1999;353(9146):9-13.
4. Effect of Metoprolol CR/XL in Chronic Heart Failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet. 1999;353(9169):2001-7.
5. Pitt D. ACE Inhibitor Co-therapy in Patients with Heart Failure: Rationale for the Randomized Aldactone Evaluation Study (RALES). Eur Heart J. 1995;16(Suppl N):107-10. doi: 10.1093/eurheartj/16.suppl_n.107.
6. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999;341(10):709-17. doi: 10.1056/NEJM199909023411001.
7. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, et al. Ivabradine and Outcomes in Chronic Heart Failure (SHIFT): A Randomised Placebo-controlled Study. Lancet. 2010;376(9744):875-85. doi: 10.1016/S0140-6736(10)61198-1.
8. Taylor AL, Ziesche S, Yancy C, Carson P, D'Agostino R Jr, Ferdinand K, et al. Combination of Isosorbide Dinitrate and Hydralazine in Blacks with Heart Failure. N Engl J Med. 2004;351(20):2049-57. doi: 10.1056/NEJMoa042934.
9. Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of Enalapril on Survival in Patients with Reduced Left Ventricular Ejection Fractions and Congestive Heart Failure. N Engl J Med. 1991;325(5):293-302. doi: 10.1056/NEJM199108013250501.
10. Pfeffer MA, Braunwald E, Moyé LA, Basta L, Brown EJ Jr, Cuddy TE, et al. Effect of Captopril on Mortality and Morbidity in Patients with Left Ventricular Dysfunction After Myocardial Infarction. Results of the Survival and Ventricular Enlargement Trial. The SAVE Investigators. N Engl J Med. 1992;327(10):669-77. doi: 10.1056/NEJM199209033271001.
11. Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, et al. Effects of Candesartan in Patients with Chronic Heart Failure and Reduced Left-ventricular Systolic Function Intolerant to Angiotensin-Converting-Enzyme Inhibitors: The CHARM-Alternative Trial. Lancet. 2003;362(9386):772-6. doi: 10.1016/S0140-6736(03)14284-5.
12. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin Inhibition Versus Enalapril in Heart Failure. N Engl J Med. 2014;371(11):993-1004. doi: 10.1056/NEJMoa1409077.
13. McMurray J, Packer M, Desai A, Gong J, Greenlaw N, Lefkowitz M, et al. A Putative Placebo Analysis of the Effects of LCZ696 on Clinical Outcomes in Heart Failure. Eur Heart J. 2015;36(7):434-9. doi: 10.1093/eurheartj/ehu455.
14. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2020;383(15):1436-46. doi: 10.1056/NEJMoa2024816.
15. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019;381(21):1995-2008. doi: 10.1056/NEJMoa1911303.
16. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. 2020;383(15):1413-24. doi: 10.1056/NEJMoa2022190.
17. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015;373(22):2117-28. doi: 10.1056/NEJMoa1504720.
18. Zannad F, Ferreira JP, Pocock SJ, Anker SD, Butler J, Filippatos G, et al. SGLT2 Inhibitors in Patients with Heart Failure with Reduced Ejection Fraction: A Meta-analysis of the EMPEROR-Reduced and DAPA-HF Trials. Lancet. 2020;396(10254):819-29. doi: 10.1016/S0140-6736(20)31824-9.
19. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, et al. SGLT2 Inhibitors for Primary and Secondary Prevention of Cardiovascular and Renal Outcomes in Type 2 Diabetes: A Systematic Review and Meta-analysis of Cardiovascular Outcome Trials. Lancet. 2019;393(10166):31-9. doi: 10.1016/S0140-6736(18)32590-X.
20. Packer M, McMurray JJV. Rapid Evidence-based Sequencing of Foundational Drugs for Heart Failure and a Reduced Ejection Fraction. Eur J Heart Fail. 2021;23(6):882-94. doi: 10.1002/ejhf.2149.
21. Vardeny O, Claggett B, Packer M, Zile MR, Rouleau J, Swedberg K, et al. Efficacy of Sacubitril/Valsartan vs. Enalapril at Lower than Target Doses in Heart Failure with Reduced Ejection Fraction: The PARADIGM-HF Trial. Eur J Heart Fail. 2016;18(10):1228-34. doi: 10.1002/ejhf.580.
22. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med. 2001;344(22):1651-8.

Personalized Treatment of Heart Failure with Reduced Ejection Fraction: Ivabradine, Nitrate/Hydralazine, and Digoxin – A Systematic Review and Meta-Analysis

Ivna Girard Cunha Vieira Lima[1] *and Edimar Alcides Bocchi*[1]

Instituto do Coração (InCor) do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HC-FMUSP),[1] *São Paulo, SP – Brazil*

Introduction

In the last 30 years, treatment of chronic heart failure with reduced ejection fraction (HFrEF) has evolved considerably, and a significant reduction was achieved in mortality over time and hospitalization rates for chronic heart failure (CHF).[1]

Neurohormonal blockade has become key in the treatment of CHF, but with the discovery of new therapies such as sodium-glucose cotransporter-2 inhibitors (SGLT2i), neprilysin inhibitors, resynchronization therapies, and new procedures, the number of treatment options in addition to standard therapy has increased considerably. However, it is known that the start of medications that reduce outcomes in CHF has historically been recommended following the order of publication of efficacy trials. Considering the many treatment options available today, a clinical question arises: is it possible to personalize additional treatments according to the patient's clinical characteristics? This meta-analysis aims to look for populations of interest where ivabradine, hydralazine and nitrate, and digoxin could have incremental beneficial effects.

Methods

This work aimed to identify, evaluate, and systematically summarize the available evidence of randomized clinical trials on ivabradine, hydralazine/isosorbide dinitrate, and digoxin in adult patients with chronic HFrEF compared with placebo or optimized medication therapy regarding outcomes of total mortality, cardiovascular mortality, and hospitalization for heart failure as determined by the Core Outcomes Measures in Effectiveness Trials; we searched for populations of interest where these drugs seemed to have better effectiveness.

Inclusion criteria

- Adults over 18 years old;
- Patients with HFrEF of any etiology;
- Randomized clinical trials;
- Subanalyses of randomized clinical trials;
- Date of publication: from 2012 on, due to the publication of studies on the effectivity of ivabradine;
- The original trials do not need to comply with the year of publication criterion.

Exclusion criteria

- Patients with heart failure and preserved ejection fraction, acute or decompensated heart failure;
- Pediatric population (< 18 years old);
- Observational studies, case reports, or pre-published protocols;
- Date of publication: prior to 2012, for post-hoc studies.

Search and sources of information

Our search was performed using the PubMed (Medline) and Virtual Health Library (BVS) databases using MeSH and DeCS descriptors for each drug of interest; the inclusion of studies in this review underwent peer analysis. Preference was given to research domains.

The search terms used in this review were:

- Ivabradine – using ("Heart Failure"[Mesh]) AND "Ivabradine"[Mesh] in English and "insuficiência cardíaca" AND ivabradina in Portuguese.
- Hydralazine and nitrate – using ("isosorbide-hydralazine combination" [Mesh] AND "Heart Failure"[Mesh] in English and "insuficiência cardíaca" AND hidralazina AND isossorbida in Portuguese.
- Digoxin – using ("Digoxin"[Mesh]) AND "Heart Failure"[Mesh] in English and "insuficiência cardíaca" AND digoxina in Portuguese.

Studies published in English and Portuguese were included in our research and a search for duplicates was initially performed for removing studies on both databases. In addition, data will be reported separately for each drug of interest. The original publication of each drug was added to the review for comparing relative risks; our search was performed using the Boolean operators "OR" and "AND."

Data collection

Data were collected by selecting studies that approached subgroups of interest in order to identify populations where the treatment could have a different performance than that displayed in the initial publication. The information of interest collected from each publication was reported and stored as tables.

Keywords

Heart Failure; Hydralazine; Nitrates; Digoxin.

Mailing Address: Ivna Girard Cunha Vieira Lima •
Av. Dr. Enéas Carvalho de Aguiar, 44. Postal Code 05403-900, Cerqueira César, São Paulo, SP - Brazil
E-mail: ivna_cunha@hotmail.com
Manuscript received January 21, 2022, revised manuscript February 01, 2022, accepted February 16, 2022

DOI: https://doi.org/10.36660/abchf.20220008

Risk of bias in each study

A limitation of systematic reviews lies in the risk of bias of the selected studies; in this meta-analysis, all studies were analyzed with the Cochrane risk of bias tool. The criteria used in this review were: analysis of selection bias, blinding, performance, detection bias, incomplete data, and reporting bias.

Data summarization and synthesis

In this meta-analysis, we used the Cochrane Handbook for Systematic Reviews of Interventions as guideline. For dichotomous outcomes, the results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). For continuous outcomes, data were grouped and described as weighted mean differences and 95% CIs. The heterogeneity of trial results was assessed through a standard chi-squared test with a significance of $p < 0.10$ and I^2 statistic with significance set at 50%. We used a Mantel-Haenszel random-effects model in our statistical analysis due to the large clinical and populational variability of the studies. Publication bias was assessed through a funnel plot. All analyses used Review Manager version 5.0 (Revman, Cochrane, Oxford, United Kingdom). p values < 0.05 were considered statistically significant. For evaluating the effect of the methodological character of studies on our results, the weight of these characteristics' components in our meta-analysis was evaluated through a sensitivity analysis.

Results

Qualitative analysis

Studies selected for assessing populations of interest were predominantly found in the search for ivabradine treatment; for this drug, all selected studies were post-hoc analyses of the original SHIFT study.

We found 207 studies in this search, which were added to 37 studies retrieved from the BVS database. We removed 131 duplicate studies. After analyzing the titles, 99 studies were selected for screening; of these, 70 were excluded after going through the inclusion and exclusion criteria. Our of the 29 remaining studies, 9 were classified after complete reading and were included in the quantitative and qualitative analyses, as shown in Figure 1.

We found 31 studies when searching for digoxin. After analyzing the titles, 16 studies were selected for screening; of these, 6 were excluded after going through the inclusion and exclusion criteria. Our of the 10 remaining studies, 3 were classified after complete reading and were included in the quantitative and qualitative analyses.

We found 16 studies when searching for the combination of hydralazine and nitrate. After analyzing the titles, 12 studies were selected for screening; of these, 9 were excluded after going through the inclusion and exclusion criteria. Our of the 3 remaining studies, 2 were classified after complete reading and were included in the quantitative analysis.

Characteristics of studies

Tables 1 and 2 summarize the characteristics of the included studies. The evaluated criteria were: sample size, percentage of male patients, inclusion criteria of each study, percentage of beta-blocker use, percentage of angiotensin-converting enzyme inhibitor (ACEI) use, percentage of diuretic use, and percentage of mineralocorticoid receptor antagonist use.

Risk of bias

All studies included in this meta-analysis were post-hoc analyses of the original SHIFT, DIG, and A-HEFT studies. The risk of selection bias was considered high in all studies, since these are trials of populations of interest; blinding bias was also considered high in all studies.

Synthesis of results

Ivabradine results

We found 9 randomized clinical trials for the composite outcome of death or hospitalization for heart failure (HF), and subpopulations of interest were: populations with Chagas disease, left bundle branch block (LBBB), advanced CHF, chronic obstructive pulmonary disease (COPD), heart rate (HR) over 77 beats per minute (bpm), who used less than 50% of the maximum beta-blocker dose, patients with diabetes, and those using carvedilol or not.

In total, the number of events for the composite outcome of death or hospitalization for HF was 2423 for the ivabradine group and 3346 for the control group; ivabradine significantly reduced the composite outcome with an OR of 0.77 ($Z = 8.32$ $p < 0.0001$ and 95% CI 0.72–0.82) and calculated heterogeneity of $I^2 = 0\%$. (Figure 2)

The number of events considering the cardiovascular death outcome was 1288 for the ivabradine group and 1727 for the control group; ivabradine significantly reduced this outcome with an OR of 0.83 ($Z = 2.91$ $p = 0.004$ and 95% CI 0.73–0.94) and calculated heterogeneity of $I^2 = 53\%$. (Figure 3)

Considering the hospitalization for CHF outcome, the number of events in the ivabradine group was 1621, in comparison with 2380 in the control group. There was a significant difference between groups, with an OR = 0.72 ($Z = 8.99$, $p = <0.00001$ and 95% CI 0.67–0.78) and calculated heterogeneity of $I^2 = 0\%$. (Figure 4)

Digoxin results

For the composite outcome of death or hospitalization for HF, we found 3 randomized clinical trials, and the study of advanced HF was added twice due to information related to patients with New York Heart Association (NYHA) class III and IV HF and ejection fraction < 25%.

In total, the number of events for the composite outcome of death or hospitalization for HF was 1495 for the digoxin group and 1748 for the control group; digoxin significantly reduced the composite outcome with an OR of 0.76 ($Z = 2.41$ $p < 0.02$ and 95% CI 0.61–0.95) and calculated heterogeneity of $I^2 = 81\%$. (Figure 5)

For the cardiovascular death outcome, the number of events was 2029 in the digoxin group and 1998 in the control group, with no significant difference between groups OR =

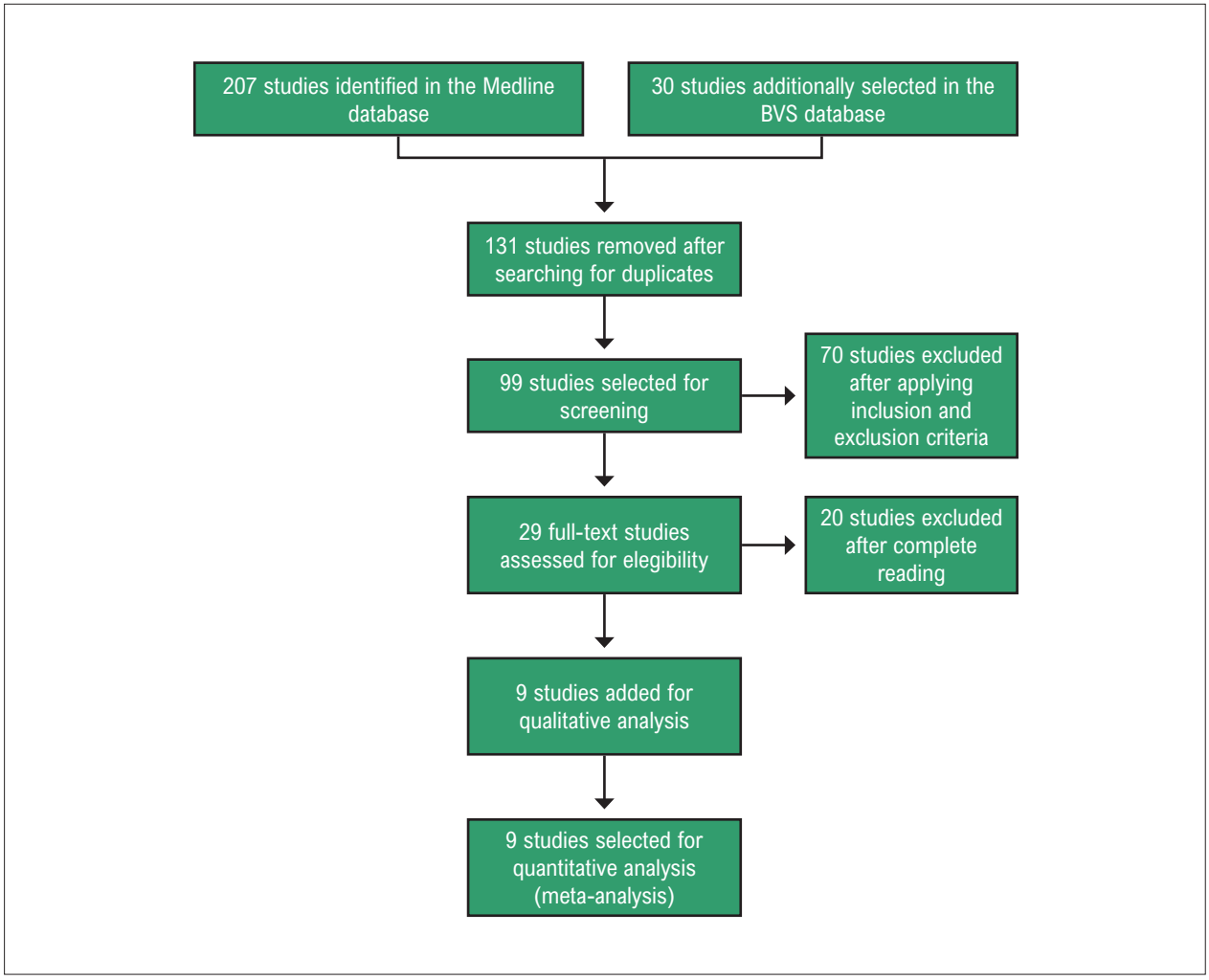


Figure 1 – *PRISMA flow diagram for the selection of studies on ivabradine.*

1.02 (Z = 0.57 p = 0.57 and 95% CI 0.95–1.10) and calculated heterogeneity of I^2 = 0%. The original study (DIG Trial) was included in this analysis. (Figure 6)

For the hospitalization for CHF outcome, the number of events in the digoxin group was 1936, in comparison with 2547 in the control group. There was a significant difference between groups, with an OR = 0.67 (Z = 7.47, p < 0.00001 and 95% CI 0.60–0.74) and calculated heterogeneity of I^2 = 47%. The original study (DIG Trial) was included in this analysis. (Figure 7)

Hydralazine/nitrate results

We found 2 populations of interest for the study of the outcomes of this drug combination: patients with atrial fibrillation and patients aged 65 years or older. The weight of these studies was small in comparison with the original A-HEFT study included in the analysis, thus our results may have been influenced by the greater number of patients in the original study.

The total number of events for the composite outcome of death or hospitalization for HF was 235 for the hydralazine/nitrate group and 324 for the control group; the combination of hydralazine and nitrate significantly reduced the composite outcome with an OR of 0.62 (Z = 4.49 p < 0.0001 and 95% CI 0.50–0.76) and calculated heterogeneity of I^2 = 0%. (Figure 8)

For the cardiovascular death outcome, the number of events was 47 in the hydralazine/nitrate group and 84 in the control group; the combination of hydralazine and nitrate significantly reduced the composite outcome with an OR of 0.54 (Z = 3.22 p < 0.001 and 95% CI 0.37–0.79) and calculated heterogeneity of I^2 = 0%. (Figure 9)

For the hospitalization for CHF outcome, the number of events in the hydralazine/nitrate group was 148, as opposed to 218 in the control group, with a significant difference between groups: OR = 0.62 (Z = 4.0, p = < 0.0001 and 95% CI 0.49–0.78) and calculated heterogeneity I^2 = 47%. The original study (A-HEFT Trial) was included in this analysis. (Figure 10)

Discussion and limitations

We performed a meta-analysis of post-hoc studies of randomized trials, searching for subpopulations of interest

Table 1 – Characteristics of the selected studies

Trial (reference)	Sample size (n)	Mean age	Male (%)	Inclusion criteria
Bouabdallaoui et al.[2]	1657	59.5 ± 11	66	HFrEF < 35%, NYHA II–IV, with HR > 77 bpm, sinus rhythm despite maximum tolerated beta-blocker dose.
Bocchi et al.[3]	20	62 ± 11	65	HFrEF < 35%, NYHA II–IV, with HR > 70 bpm, sinus rhythm despite maximum tolerated beta-blocker dose. Patients with Chagas disease.
Komajda et al.[4]	1979	62 ± 9.8	75	HFrEF < 35%, NYHA II–IV, with HR > 70 bpm, sinus rhythm despite maximum tolerated beta-blocker dose. Patients with diabetes.
Bocchi et al.[5]	1318	59.3 ± 11	77	HFrEF < 35%, NYHA II–IV, with HR > 70 bpm, sinus rhythm despite maximum tolerated beta-blocker dose. Patients using carvedilol.
Borer et al.[6]	712	60 ± 12.2	77	NYHA IV HFrEF or EF < 20% with HR > 70 bpm, sinus rhythm despite maximum tolerated beta-blocker dose.
Tavazzi L et al.[7]	730	65.2 ± 9.5	81	HFrEF < 35%, NYHA II–IV, with HR > 70 bpm, sinus rhythm despite maximum tolerated beta-blocker dose. Patients with COPD.
Reil et al.[8]	912	62 ± 10.6	69	HFrEF < 35%, NYHA II–IV, with HR > 70 bpm, sinus rhythm despite maximum tolerated beta-blocker dose. Patients with LBBB.
Swedberg K et al.[9]	1624	60 ± 11.5	77.2	HFrEF < 35%, NYHA II–IV, with HR < 70 bpm, sinus rhythm beta-blocker dose.
Mihai Gheorghiade et al.[10]	1118	65 ± 11	81	Patients with EF < 25% and HF diagnosis.
Mihai Gheorghiade et al.[11]	1127	63 ± 11	73	Patients with EF < 45% with a diagnosis of NYHA III and IV HF.
Azimil Abdul-Rahim et al.[12]	1195	64 ± 10.6	71.1	Patients with EF < 45% were enrolled in an auxiliary study performed in parallel with the main trial.
Azimil Abdul-Rahim et al.[13]	1933	64.2	73.6	Patients with diabetes, EF ≤ 45%, and sinus rhythm. HF diagnosis was based on current or past clinical symptoms (activity limitation, fatigue and dyspnea or orthopnea), signs (edema, elevated jugular venous pressure, stertor, or gallop rhythm), or radiological evidence of pulmonary congestion.
Mitchell JE et al.[14]	183	61 ± 12	68	NYHA class III or IV for at least 3 months – subpopulation with AF. Evidence of left ventricular dysfunction in the 6 months prior to randomization and EF < 35% or rest EF < 45% with LVEDD < 2.9 cm/m^2 of body surface area or > 6.5 cm at echocardiography.
Taylor AL et al.[15]	157	72 ± 5.7	52	NYHA III or IV for at least 3 months – subpopulation aged 65 years and older. Evidence of left ventricular dysfunction in the 6 months prior to randomization and EF < 35% or rest EF < 45% with LVEDD < 2.9 cm/m^2 of body surface area or > 6.5 cm at echocardiography.
Taylor AL et al.[16]	1050	56 ± 12.7	55.8	Afro-descendants with NYHA class III or IV HF for at least 3 months – evidence of left ventricular dysfunction in the 6 months prior to randomization and EF < 35% or rest EF < 45% with LVEDD < 2.9 cm/m^2 of body surface area or > 6.5 cm at echocardiography.

HFrEF: heart failure with reduced ejection fraction; NYHA: New York Heart Association; HR: heart rate; EF: ejection fraction; AF: atrial fibrillation; COPD: chronic obstructive pulmonary disease; LBBB: left bundle branch block; LVEDD: left ventricular end-diastolic diameter.

Table 2 – Characteristics of the selected studies

Trial (reference)	Beta-blocker use (%)	ACEI use (%)	Diuretic use (%)	Spironolactone use (%)
Bouabdallaoui, Nadia et al.[2]	86.1	89.7	---	63.1
Bocchi et al.[3]	90	56	94	83
Komadja et al.[4]	90	91	86	---
Bocchi et al.[5]	100	77	88	70
Borer et al.[6]	87	78	90	---
Tavazzi L et al.[7]	68	80	91	---
Reil et al.[8]	89.9	77	90.6	---
Swedberg K et al.[9]	100	78.6	82.1	62.1
Mihai Gheorghiade et al.[10]	---	95	88	---
Mihai Gheorghiade et al.[11]	---	95	84	---
Azimil Abdul-Rahim et al.[12]	---	90.5	70.4	7.6
Azimil Abdul-Rahim et al.[13]	---	94.9	84.7	7.8
Mitchell JE et al.[14]	83	89	94	38
Taylor AL et al.[15]	76.4	63.7	89.2	37.6
Taylor AL et al.[16]	74.1	69.4	88	40.2

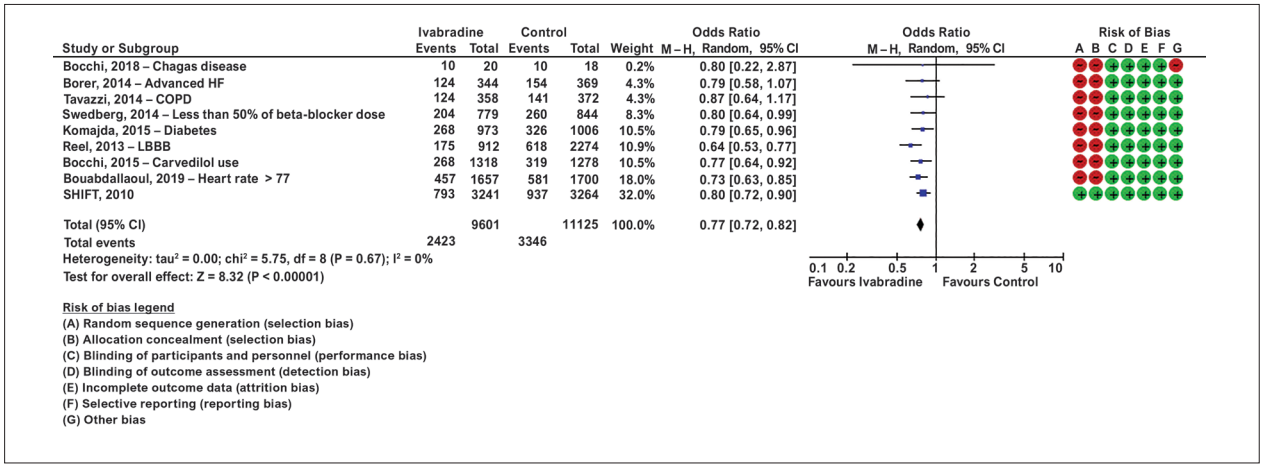


Figure 2 – *Forest plot for the composite outcome of death and hospitalization regarding ivabradine and analysis of study bias. M-H: Mantel-Haenszel.*

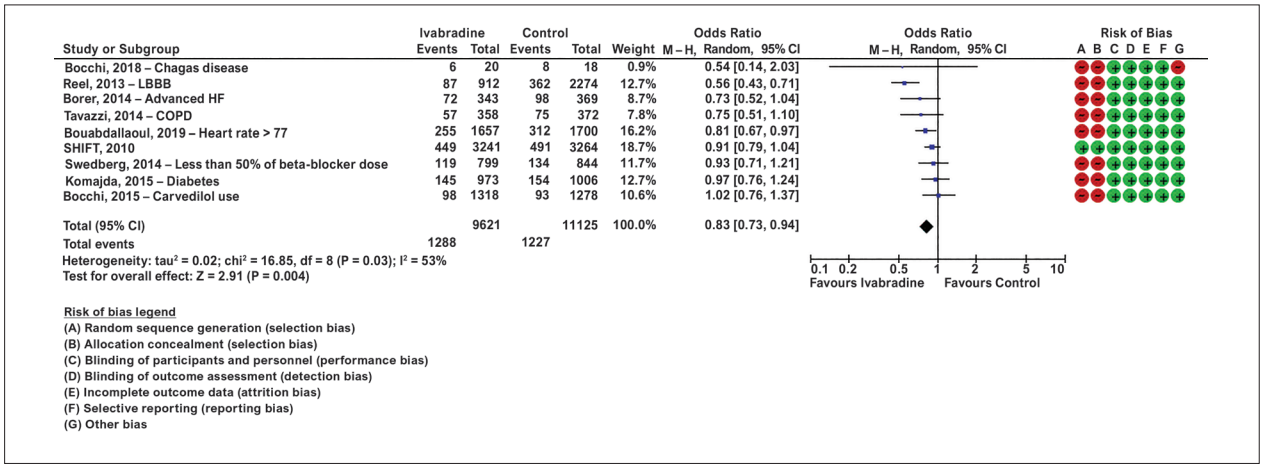


Figure 3 – *Forest plot for the cardiovascular death outcome regarding ivabradine and analysis of study bias. M-H: Mantel-Haenszel.*

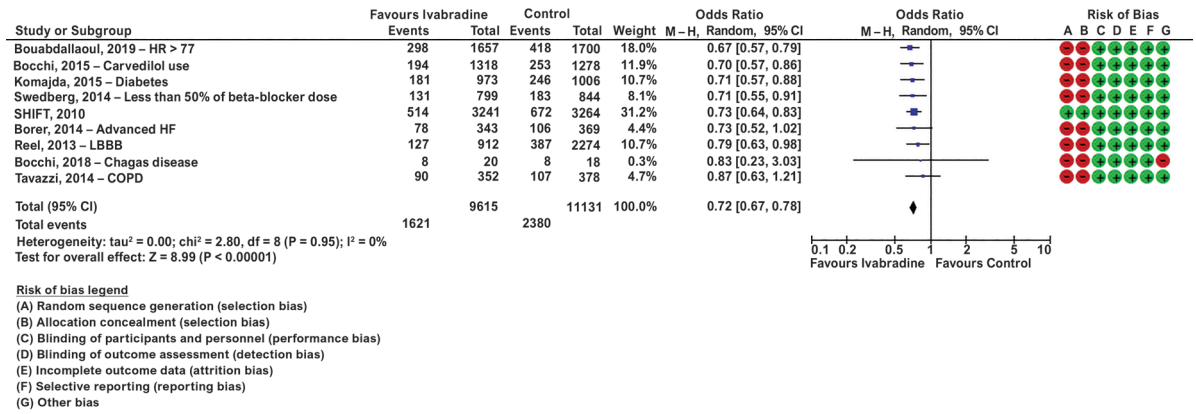


Figure 4 – *Forest plot for the composite outcome of hospitalization for CHF regarding ivabradine and analysis of study bias. M-H: Mantel-Haenszel.*

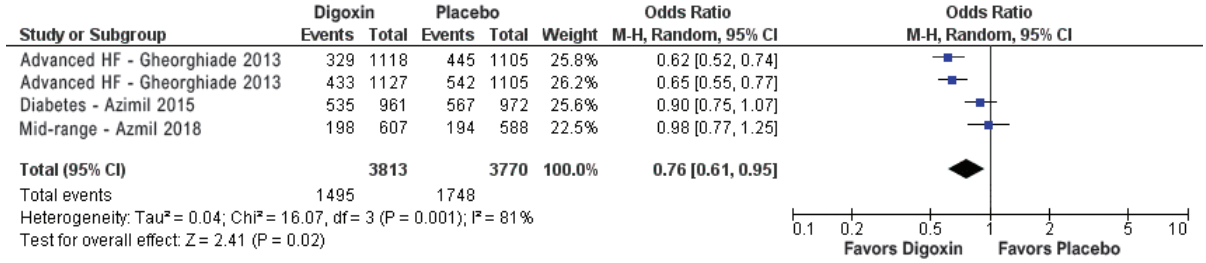


Figure 5 – *Forest plot for the composite outcome regarding digoxin. M-H: Mantel-Haenszel.*

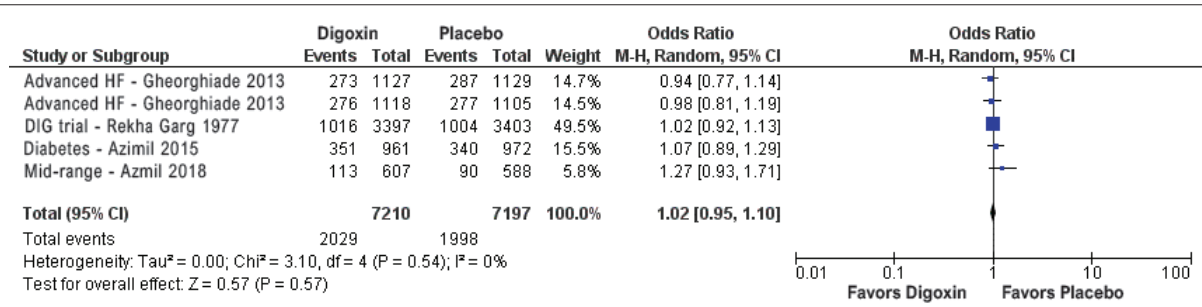


Figure 6 – *Forest plot for the cardiovascular death outcome regarding digoxin. M-H: Mantel-Haenszel.*

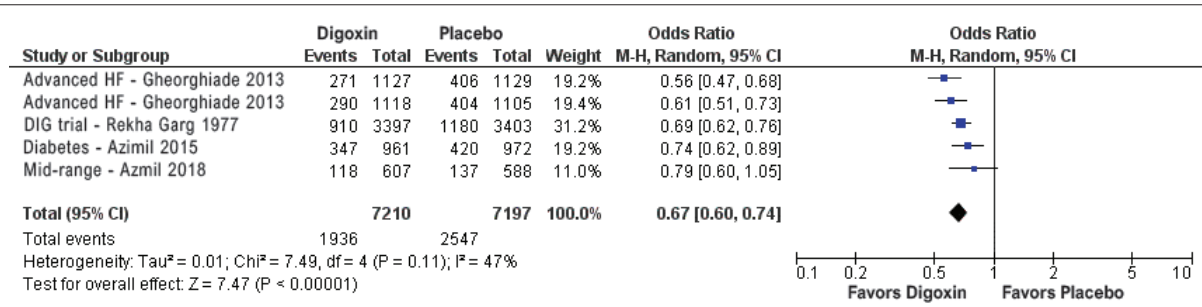


Figure 7 – *Forest plot for the outcome of hospitalization for HF regarding digoxin. M-H: Mantel-Haenszel.*

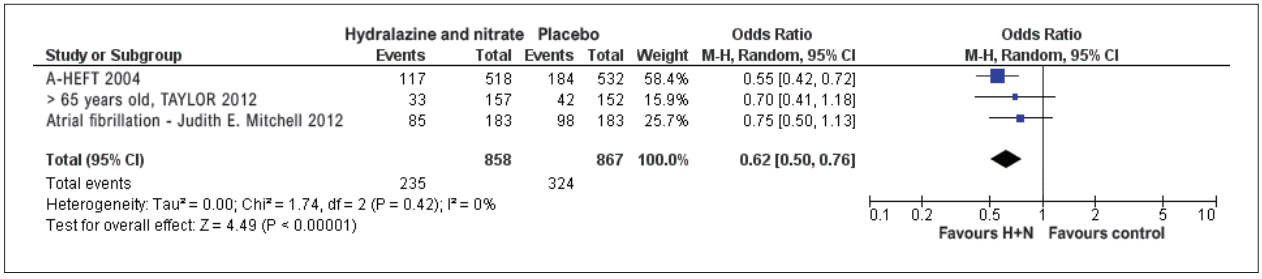


Figure 8 – *Forest plot for the composite outcome regarding the combination of hydralazine and nitrate. M-H: Mantel-Haenszel.*

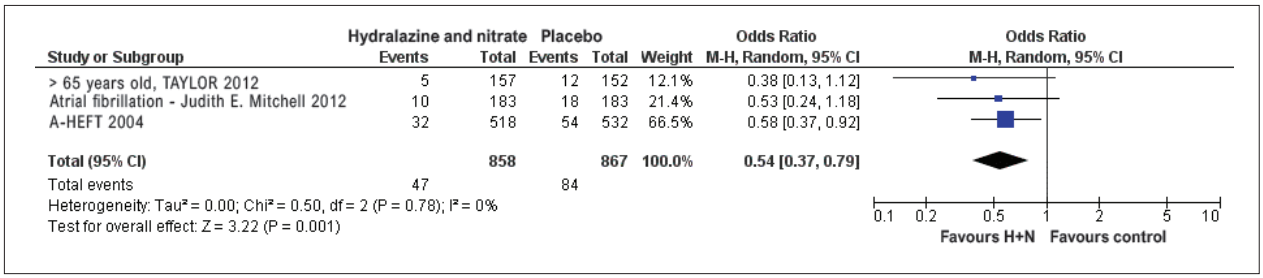


Figure 9 – *Forest plot for the cardiovascular death outcome regarding the combination of hydralazine and nitrate. M-H: Mantel-Haenszel.*

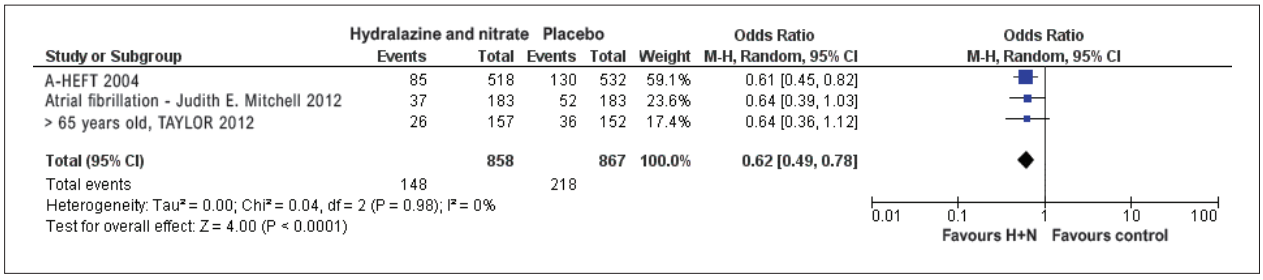


Figure 10 – *Forest plot for the outcome of hospitalization for HF regarding the combination of hydralazine and nitrate. M-H: Mantel-Haenszel.*

where the drugs ivabradine, hydralazine/nitrate, and digoxin could have better performances than in the general population of the initial SHIFT (ivabradine), A-HEFT (hydralazine and nitrate), and DIG (digoxin) trials. This was an attempt to find an improved manner of personalizing the current treatment of chronic HFrEF.

For the composite outcome of death or hospitalization for CHF, ivabradine had a similar effect measure in most subgroups. On the other hand, the performance of this drug was superior in patients with diabetes, those who did not tolerate more than 50% of the maximum beta-blocker dose, patients with LBBB, patients who did not use carvedilol, or those with HR over 77 bpm than in the general population. This showed a potential benefit of the medication related to the control of HR, which is an important marker of risk of death in patients with HFrEF. It is important to note that, for the cardiovascular death outcome, we found a heterogeneity > 50% among studies.

A consistent reduction was observed in the hospitalization for HF outcome in patients who used digoxin; in the population with advanced HF (patients with NYHA class III and IV HF and ejection fraction < 25%), the performance of this drug was superior than in the original study. However, when considering cardiovascular mortality, our analysis could not find a subpopulation where this medication showed benefits or a superior performance when compared to the DIG trial. The possible benefit in hospitalization found with the use of digitalis compounds in patients with advanced HF may stem from multiple mechanisms; one possible explanation is the positive inotropic mechanism of glycosides, in addition to the control of HR. On the other hand, it is important to highlight that the benefit of this treatment may have been dampened by possible side effects related to medication toxicity; safety outcomes were not assessed in this study.

For the combination of hydralazine and nitrate, beneficial effects had large CIs in both identified populations, leading to speculations regarding a possible effect of chance on our findings. However, in the afro-descendant population included in the A-HEFT trial (used for comparison), this drug combination was able to reduce the composite outcome of death and hospitalization in a consistent manner when compared to the control group, favoring this recommendation as stated by previous guidelines.

Conclusion

The aim of this meta-analysis was not to substitute the classical indications of drugs as already stated by guidelines, but instead to find subpopulations of interest; to the best of our knowledge, this search strategy is innovative.

Considering the composite outcome, the performance of ivabradine was superior in patients with diabetes, those who did not tolerate more than 50% of the maximum beta-blocker dose, patients with LBBB, those who did not use carvedilol, or those with HR over 77 bpm than in the general population. For the hospitalization outcome, the performance of digoxin was superior in the population with advanced HF (NYHA class III and IV and ejection fraction < 25%) than in the original study. Finally, for the combination of hydralazine and nitrate and composite outcome, the studied populations showed similar beneficial effects to the original study.

Author Contributions

Conception and design of the research, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Lima IGCV, Bocchi EA; Acquisition of data, Analysis and interpretation of the data and Statistical analysis: Lima IGCV.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Abdin A, Bauersachs J, Frey N, Kindermann I, Link A, Marx N, et al. Timely and Individualized Heart Failure Management: Need for Implementation Into the New Guidelines. Clin Res Cardiol. 2021;110(8):1150-8. doi: 10.1007/s00392-021-01867-2.
2. Bouabdallaoui N, O'Meara E, Bernier V, Komajda M, Swedberg K, Tavazzi L, et al. Beneficial Effects of Ivabradine in Patients with Heart Failure, Low Ejection Fraction, and Heart Rate Above 77 b.p.m. ESC Heart Fail. 2019;6(6):1199-207. doi: 10.1002/ehf2.12513.
3. Bocchi EA, Rassi S, Guimarães GV. Safety Profile and Efficacy of Ivabradine in Heart Failure Due to Chagas Heart Disease: A Post Hoc Analysis of the SHIFT Trial. ESC Heart Fail. 2018;5(3):249-56. doi: 10.1002/ehf2.12240.
4. Komajda M, Tavazzi L, Francq BG, Böhm M, Borer JS, Ford I, et al. Efficacy and Safety of Ivabradine in Patients with Chronic Systolic Heart Failure and Diabetes: an Analysis from the SHIFT Trial. Eur J Heart Fail. 2015;17(12):1294-301. doi: 10.1002/ejhf.347.
5. Bocchi EA, Böhm M, Borer JS, Ford I, Komajda M, Swedberg K, et al. Effect of Combining Ivabradine and β-Blockers: Focus on the Use of Carvedilol in the SHIFT Population. Cardiology. 2015;131(4):218-24. doi: 10.1159/000380812.
6. Borer JS, Böhm M, Ford I, Robertson M, Komajda M, Tavazzi L, et al. Efficacy and Safety of Ivabradine in Patients with Severe Chronic Systolic Heart Failure (from the SHIFT study). Am J Cardiol. 2014;113(3):497-503. doi: 10.1016/j.amjcard.2013.10.033.
7. Tavazzi L, Swedberg K, Komajda M, Böhm M, Borer JS, Lainscak M, et al. Clinical Profiles and Outcomes in Patients with Chronic Heart Failure and Chronic Obstructive Pulmonary Disease: An Efficacy and Safety Analysis of SHIFT Study. Int J Cardiol. 2013;170(2):182-8. doi: 10.1016/j.ijcard.2013.10.068.
8. Reil JC, Robertson M, Ford I, Borer J, Komajda M, Swedberg K, et al. Impact of Left Bundle Branch Block on Heart Rate and its Relationship to Treatment with Ivabradine in Chronic Heart Failure. Eur J Heart Fail. 2013;15(9):1044-52. doi: 10.1093/eurjhf/hft072.
9. Swedberg K, Komajda M, Böhm M, Borer J, Robertson M, Tavazzi L, et al. Effects on Outcomes of Heart Rate Reduction by Ivabradine in Patients with Congestive Heart Failure: Is there an Influence of Beta-blocker Dose?: Findings from the SHIFT (Systolic Heart Failure Treatment with the I(f) Inhibitor Ivabradine Trial) Study. J Am Coll Cardiol. 2012;59(22):1938-45. doi: 10.1016/j.jacc.2012.01.020.
10. Gheorghiade M, Vaduganathan M, Fonarow GC, Greene SJ, Greenberg BH, Liu PP, et al. Anticoagulation in Heart Failure: Current Status and Future Direction. Heart Fail Rev. 2013;18(6):797-813. doi: 10.1007/s10741-012-9343-x.
11. Gheorghiade M, Vaduganathan M, Ambrosy A, Böhm M, Campia U, Cleland JG, et al. Current Management and Future Directions for the Treatment of Patients Hospitalized for Heart Failure with Low Blood Pressure. Heart Fail Rev. 2013;18(2):107-22. doi: 10.1007/s10741-012-9315-1.
12. Abdul-Rahim AH, Shen L, Rush CJ, Jhund PS, Lees KR, McMurray JJV. Effect of Digoxin in Patients with Heart Failure and Mid-range (borderline) Left Ventricular Ejection Fraction. Eur J Heart Fail. 2018;20(7):1139-45. doi: 10.1002/ejhf.1160.
13. Abdul-Rahim AH, MacIsaac RL, Jhund PS, Petrie MC, Lees KR, McMurray JJ. Efficacy and Safety of Digoxin in Patients with Heart Failure and Reduced Ejection Fraction According to Diabetes Status: An Analysis of the Digitalis Investigation Group (DIG) Trial. Int J Cardiol. 2016;209:310-6. doi: 10.1016/j.ijcard.2016.02.074.
14. Mitchell JE, Tam SW, Trivedi K, Taylor AL, O'Neal W, Cohn JN, et al. Atrial Fibrillation and Mortality in African American Patients with Heart Failure: Results from the African American Heart Failure Trial (A-HeFT). Am Heart J. 2011;162(1):154-9. doi: 10.1016/j.ahj.2011.04.022.
15. Taylor AL, Sabolinski ML, Tam SW, Ziesche S, Ghali JK, Archambault WT, et al. Effect of Fixed-dose Combined Isosorbide Dinitrate/Hydralazine in Elderly Patients in the African-American Heart Failure Trial. J Card Fail. 2012;18(8):600-6. doi: 10.1016/j.cardfail.2012.06.526.
16. Taylor AL, Ziesche S, Yancy C, Carson P, D'Agostino R Jr, Ferdinand K, et al. Combination of Isosorbide Dinitrate and Hydralazine in Blacks with Heart Failure. N Engl J Med. 2004;351(20):2049-57. doi: 10.1056/NEJMoa042934.

New Drugs for Treatment of Heart Failure with Reduced Ejection Fraction: Vericiguat and Omecamtiv Mecarbil

Mucio Tavares de Oliveira Jr.,[1] *Antonio Carlos Pereira Barretto,*[1] *Carlos Henrique Del Carlo,*[1] *Sergio Jallad,*[1] *Mariana Silveira de Alcantara Chaud*[1]

Instituto do Coração – Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP),[1] *São Paulo, SP – Brazil*

The last decades have witnessed a decline in the mortality of patients with heart failure with reduced ejection fraction (HFrEF), comparing the periods from 1987 to 1991, from 1992 to 1996, and from 1997 to 2001, but this did not occur when comparing patients with heart failure with preserved ejection fraction (HFpEF) between the same periods.[1] More recently, a study with more than 11,000 hospitalized patients (3 or 6 months) reaffirmed that hospitalization of patients with left ventricular ejection fraction (LVEF) < 45% contributes to increased mortality and morbidity, especially within the first 3 months (56% of hospitalizations). Mortality was 22.5% at 2 years. It became clear once again that the presence of comorbidities increases the occurrence of worsening, and renal dysfunction especially increases the instability of heart failure (HF) 2-fold. In the entire sample, triple therapy was detected in only 14% of patients, and 1 in 6 patients evolved with worsening HF within 18 months of follow-up.[2]

The past 2 or 3 years have seen the development and approval of new therapeutic options, especially drug therapies, which significantly improve survival and significantly reduce hospitalization or readmission of patients with HFrEF (PARADIGM, EMPEROR-Reduced, DAPA-HF).

Nevertheless, there is still a great deal of room for new therapies that improve survival, in addition to reducing the chance of progression to instability and the need for hospitalization or visits to emergency units to treat decongestion, without requiring subsequent hospitalization. In spite of the development and approval of new drugs, devices, and surgical treatments for HFrEF and also very recently for the stability of HFpEF, there is still a need for new means to treat these patients.

In this article, we will address 2 new drugs with new mechanisms of action that have increased our possibility of stabilizing these patients, as well as future evidence of improved prognosis.

Keywords

Insuficiência Cardíaca; Sobrevida; Hospitalização; Omecamtiv Mecarbil; Vericiguat.

Mailing Address: Mucio Tavares de Oliveira Jr. •
Rua Itapeva, 202, conj 85 a 89. Postal Code 01332-000, São Paulo, SP – Brazil
E-mail: mucio@incor.usp.br
Manuscript received February 08, 2022, revised manuscript February 14, 2022, accepted March 02, 2022

DOI: https://doi.org/10.36660/abchf.20220009

Omecamtiv mecarbil - myosin activator

During the 1980s and 1990s, several attempts at long-term treatment with inotropes in patients with systolic dysfunction almost always resulted in increased mortality or a neutral effect (oral milrinone, intravenous dobutamine infusion), with the exception of levosimendan, when used in intermittent infusions in patients with advanced heart failure, which did not interfere with prognosis and avoided worsening quality of life and readmissions.[3]

Omecamtiv mecarbil is an inotropic agent whose mechanism of action differs from the others, having no relation to increased calcium influx or increased sensitivity to calcium by myocardial fibers. The drug increases cardiac contractility by selectively interacting with cardiac myosin, increasing the number of molecules available to bind to actin and produce greater kinetic energy at the beginning of systole, without increasing calcium and/or oxygen consumption. Omecamtiv mecarbil binds to a site that stabilizes the molecule, promoting a greater number of actin-myosin interactions, increasing the amount of energy generated with each ventricular systole.[4]

Pre-clinical studies have demonstrated a significant improvement in increased cardiac output, improved myocardial tension, decreased end-systolic and end-diastolic volumes, improved LVEF, and reduced natriuretic peptides.[5]

The Global Approach to Lowering Adverse Cardiac Outcomes through Improving Contractility in Heart Failure (GALACTIC-HF) study[6] evaluated whether oral treatment with omecamtiv mecarbil in patients with HFrEF reduced the risk of HF events and cardiovascular death.

The study included a total 8,256 patients between 18 and 85 years of age, New York Heart Association functional class (NYHA FC) II, III, or IV, and LVEF 35% or lower. Patients were hospitalized for HF, had been treated in the emergency department, or had been hospitalized for HF within 1 year. Patients were required to have N-terminal pro–B-type natriuretic peptide (NT-proBNP) of at least 400 pg/mL or B-type natriuretic peptide (BNP) of at least 125 pg/mL; in those with atrial fibrillation or flutter, the NT-proBNP cut-off level was 1,200 pg/mL, and the BNP cut-off level was 375 pg/mL. Other drug interventions or devices could be indicated according to the investigator.

The primary composite endpoint was a HF event (emergency room visit or hospitalization due to HF) or cardiovascular death, and secondary endpoints were cardiovascular death, change in Kansas City Cardiomyopathy Questionnaire (KCCQ) score, first hospitalization for HF, and all-cause death.

Randomization was 1:1 to placebo or omecamtiv mecarbil at doses of 25 mg, 37.5 mg, or 50 mg twice daily according to the drug plasma level.

Average age of patients was 64 years. A quarter of patients were included during hospitalization; 96% were in NYHA FC II or III. Mean systolic pressure was 116 mmHg; mean LVEF was 26%. NT-proBNP was 2000 pg/mL, and glomerular filtration rate was 58 ml/min/1.73 m^2. The prescription of drugs that change prognosis was high (4% with angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, or angiotensin receptor-neprilysin inhibitor and 94% with beta-blocker), but sodium-glucose co-transporter 2 inhibitor was still in a small proportion (2.5%). The results demonstrated a reduction in the primary composite outcome of 37% in the omecamtiv mecarbil group and 39% in the placebo group (OR: 0.92; 0.86 to 0.99; p = 0.03), but there was no difference in the secondary outcomes of cardiovascular death (19.6% versus 19.4%; OR: 1.01; 0.92 to 1.11), change in KCCQ, hospitalization for HF, or emergency room visit for HF (27.7% versus 28.7%). The omecamtiv mecarbil group had a 10% reduction in median NT-proBNP (Figure 1).

Post-hoc analysis analyzed the results of the GALACTIC-HF study according to the following LVEF quartiles: ≤ 22% (n = 2,246), from 23% to 28% (n = 2210), from 29% to 32% (n = 2,026), and ≥ 33% (n = 1,750).[7] Patients in the omecamtiv mecarbil group with lower LVEF had a 17% relative risk reduction for the primary outcome (EF ≤ 22%; OR: 0.83; 95% confidence interval: 0.73 to 0.95) compared to patients with EF ≥ 33% (OR: 0.99; 95% confidence interval: 0.84 to 1.16; interaction as EF by quartiles, p = 0.013). However, the most significant finding was the reduction in first HF events in patients with lower LVEF. In patients with EF ≥ 33%, it was 26% versus 24% (OR 1.04; 0.86 to 1.25), and, in patients with LVEF ≤ 22%, it was 31% in the omecamtiv mecarbil group and 37% in the placebo group (OR: 0.81; confidence interval: 0.70 to 0.93).

Conclusion: These results suggest that omecamtiv mecarbil may be a useful drug in patients with more severe disease or patients at greater risk of death or HF instability.

Vericiguat

Drugs that modulate evolution and survival in HF include vasodilators, which stimulate the production of nitric oxide, but they are not the only ones, given that other drugs that also change the evolution used to this end increase production. However, there was no success, for example, with phosphodiesterase-5 inhibitors or with synthetic BNP, and those vasodilators considered effective have the characteristic of inducing tachyphylaxis. New vasodilators can be very useful for patients with HF and, to this end, vericiguat was developed and tested.

Vericiguat is a drug that stimulates soluble guanylate cyclase by binding at a site independent of nitric oxide, increasing the activity of the cyclic guanosine monophosphate pathway and endogenous production of nitric oxide, also stabilizing the binding of nitric oxide to its binding site[8,9] (Figure 2). A drug that increases the availability of nitric oxide tends to have a positive impact on HF, given that NO2 depletion is part of the pathophysiology of ventricular dysfunction, leading to vasoconstriction, vascular stiffness, stimulation of fibrosis, ventricular remodeling, and retention of sodium and water.

The drug then appeared to be a viable and potentially promising alternative; therefore, several studies were developed to study its effect in patients with both HFrEF and HFpEF.

The Global Study in Subjects with Heart Failure with Reduced Ejection Fraction (VICTORIA),[11] evaluated the

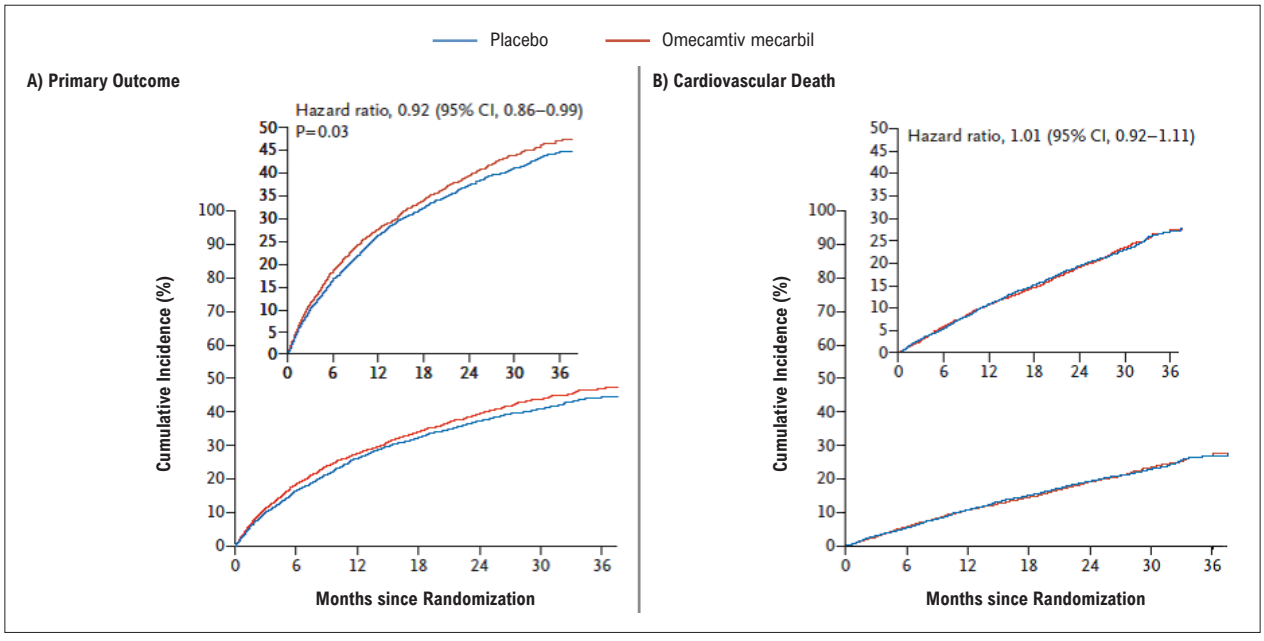


Figure 1 – *Primary and secondary outcomes of cardiovascular death of the GALACTIC-HF study.*

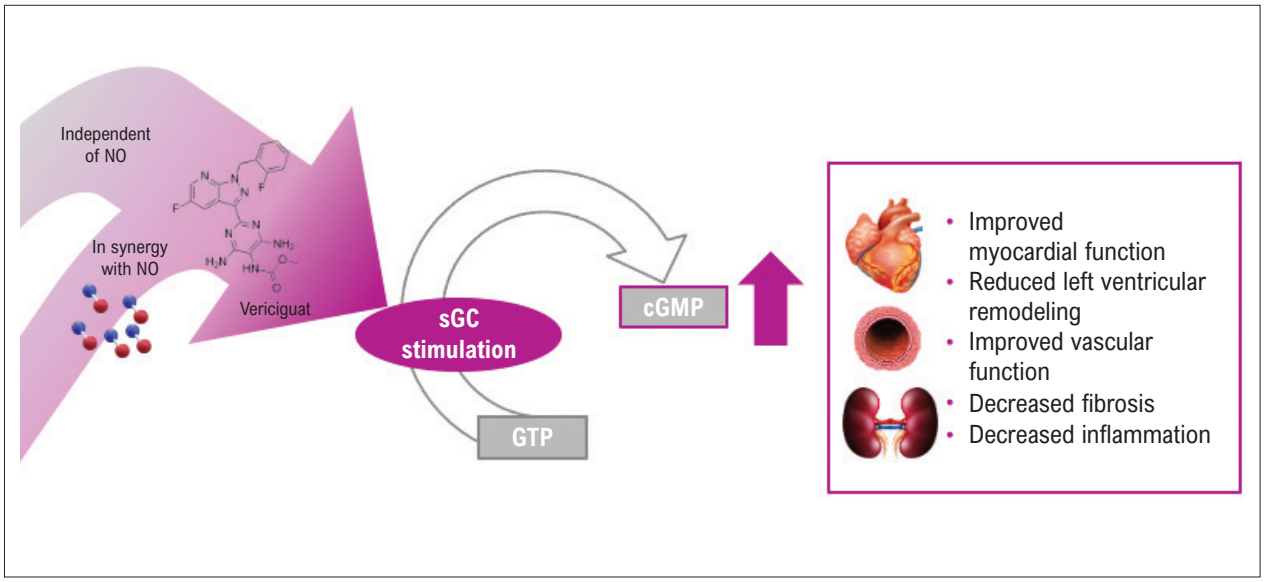


Figure 2 – *Mechanism of action of vericiguat (adapted from Armstrong et al.[9] and Gheorghiade et al.[10])*

efficacy and safety of vericiguat in patients with reduced EF and chronic HF with recent decompensation. They included 5,050 patients over 18 years of age, with HF in NYHA FC II, III, or IV and LVEF below 45% up to 12 months before randomization, BNP of 300 pg/mL or more and NT-proBNP of 1,000 pg/mL or more, and, in patients with atrial fibrillation, BNP of at least 500 pg/mL and NT-proBNP of at least 1,600 pg/mL. Evidence of worsening HF was assessed in the following 3 situations: hospitalized within 3 months before randomization, hospitalized from 3 to 6 months, and received intravenous administration within 3 months, but without hospitalization. Patients with glomerular filtration rate lower than 30 mL/min/1.73 m^2, between 15 and 30, but limited to 15% of the sample, were also included. Patients were randomized 1:1 to receive 2.5 mg vericiguat or placebo; doses increased to 5 mg and finally to the target dose of 10 mg once daily, according to blood pressure and clinical symptoms. Standard drug therapy for HF was balanced in both groups, and 60% of patients were on triple therapy (a beta-blocker, a mineralocorticoid antagonist, and an angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, or angiotensin receptor-neprilysin inhibitor), with 15% using an angiotensin receptor-neprilysin inhibitor. Median dose was 9.2 mg in both the vericiguat and placebo groups, but, at 12 months, about 90% of patients were receiving the target dose of 10 mg.

Median age was 67 years; two thirds of patients were within 3 months of hospitalization; 40% were in NYHA FC III and 59% in NYHA FC II. Mean LVEF was 29%, and mean NT-proBNP level was 2,816 pg/mL.

The primary outcome, cardiovascular death or first hospitalization for HF, occurred in 35.5% in the vericiguat group and 38.5% in the placebo group (OR: 0.90; 0.82 to 0.98; p = 0.02). Cardiovascular death occurred in 16.4% in the vericiguat group and 17.5% in the placebo group (OR: 0.93; 0.81 to 1.06). Hospitalization for HF occurred in 27.4% in the vericiguat group and 29.6% in the placebo group (OR: 0.90; 0.81 to 1.00), but, regarding total hospitalizations and recurrent hospitalizations for HF, there were 1,223 hospitalizations (38.3 events per 100 patient-years) in the vericiguat group and 1,336 hospitalizations (42.4 events per 100 patient-years) in the placebo group (OR: 0.91; 0.84 to 0.99; p = 0.02). All-cause death occurred in 20.3% in the vericiguat group and in 21.2% in the placebo group (OR: 0.95; 0.84 to 1.07; p = 0.38). A secondary outcome, all-cause death or first hospitalization for HF, occurred in 37.9% in the vericiguat group and in 40.9% in the placebo group (OR: 0.90; 0.83 to 0.98; p = 0. 02) (Figure 3).

The benefits were similar in all strata, including different LVEF. Serious adverse events occurred in a considerable number, approximately one third of the patients, but this was the same in the vericiguat and placebo groups; serious and non-serious events also occurred in 80% in both groups, here undoubtedly caused by the severity of the patients included.

A relevant finding is that, in the VICTORIA study, there were more patients with HF in NYHA FC III or IV compared to the PARADIGM and DAPA-HF studies, and the level of NT-proBNP in the patients of the VICTORIA study was almost double, which may have attenuated the benefits.

The results of the VICTORIA study provide us with an additional tool for stabilizing patients with advanced HF, progressive worsening of the disease, or refractory patients.

Other studies with vericiguat include the Soluble Guanylate Cyclase Stimulator in Heart Failure with Reduced Ejection Fraction Study (SOCRATES-REDUCED), whose primary objective was the reduction of NT-proBNP by week 12.[12] Although there was no benefit in the primary outcome, exploratory analysis suggested that, at the highest doses, there was a significant reduction in NT-proBNP.

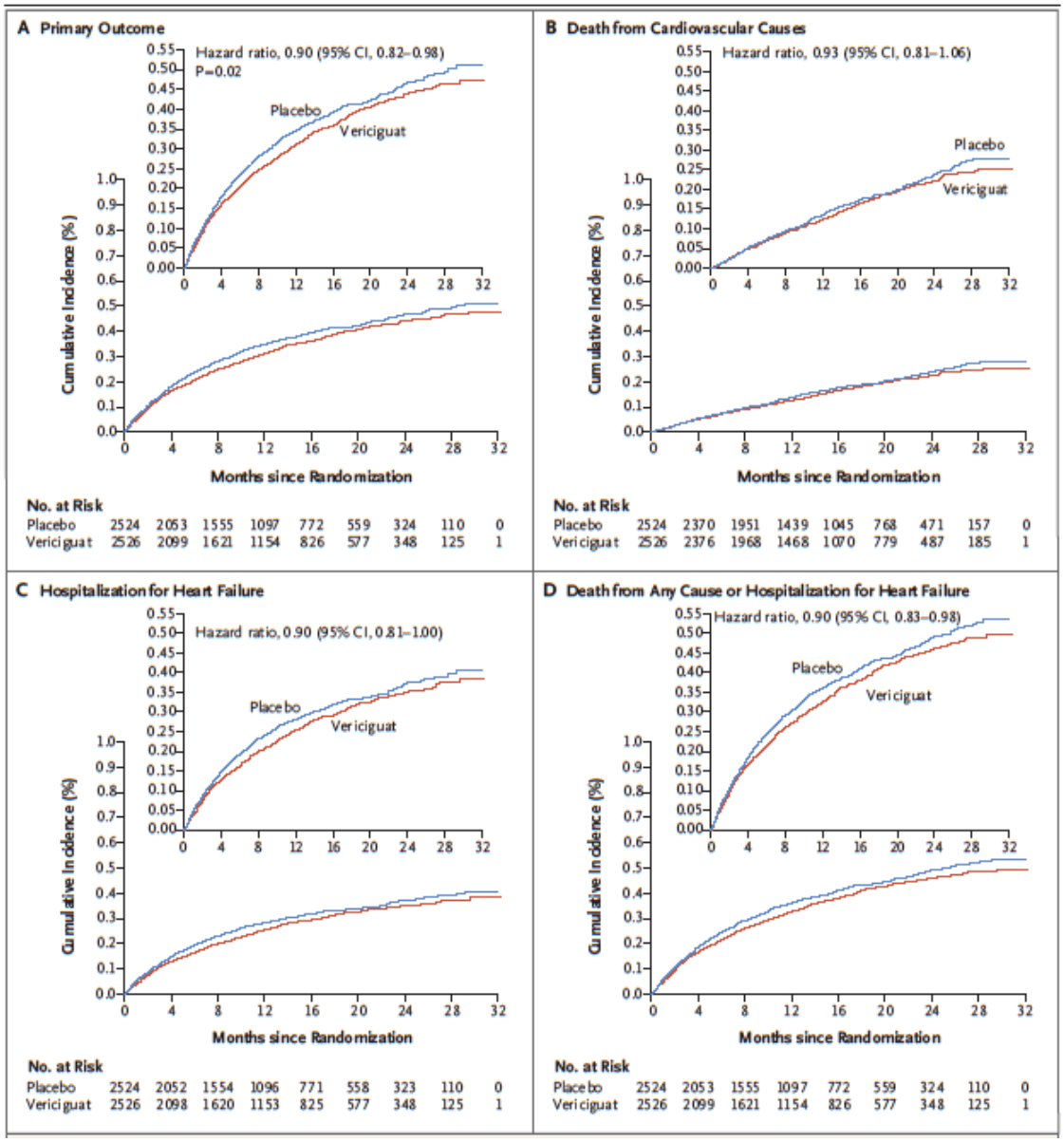


Figure 3 – *Estimates of the incidence of the primary and secondary outcomes.*

Another exploratory analysis, from the VICTORIA study, evaluated the effect of vericiguat on the evolution of renal function, and the authors concluded that the evolution of renal function was similar between patients treated with vericiguat and placebo.[13]

Vericiguat has also been tested in patients with HFpEF. The objective of the SOluble guanylate Cyclase stimulatoR in heArT failurE patientS with PRESERVED ejection fraction study (SOCRATES-PRESERVED) was to determine the dose of vericiguat in symptomatic patients with LVEF ≥ 45%, with the primary outcome of change in NT-proBNP and left atrial volume. To do this, doses were given once a day at 1.25 or 2.5 mg, or 5 or 10 mg titrated from an initial dose of 2.5 mg, or placebo for 12 weeks. Patients had mean age of 73 years, mean LVEF 57%, and atrial fibrillation 40%. At all dosages, the variation in NT-proBNP and left atrial volume were not different from patients in the placebo group. Vericiguat was well tolerated with little discontinuation. Quality of life was also assessed using the KCCQ and the score improved in the vericiguat 10 mg arm by 19.3 ± 16.3 points compared to baseline (p = 0.016).[13]

Another study, Vericiguat vs Placebo on Quality of Life in Patients With Heart Failure and Preserved Ejection Fraction (VITALITY-HFpEF)[14] analyzed 789 patients with mean age

of 73 years, mean LVEF of 56%, and mean NT-proBNP of 1,403 pg/mL. They were randomized to 15 mg or 10 mg daily of vericiguat or placebo, and the KCCQ scores in relation to the baseline and the 6-minute walk test showed no difference after 24 weeks of follow-up. Once again the drug was well tolerated.

Conclusion: Vericiguat is a drug that has shown benefits when used at an adequate dose for patients with HFrEF, and it will certainly be a new therapeutic tool for patients with progressive HF, patients with repeated hospitalizations or emergency room visits, and in patients at a higher risk of death or hospitalization. There is still a lack of data to support its use in patients with HFpEF.

Author Contributions

Conception and design of the research, Acquisition of data and Analysis and interpretation of the data: Oliveira Jr. MT; Writing of the manuscript and Critical revision of the manuscript for intellectual contente: Oliveira Jr. MT, Barretto ACP, Del Carlo CH, Jallad S, Chaud MAS.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in Prevalence and Outcome of Heart Failure with Preserved Ejection Fraction. N Engl J Med. 2006;355(3):251-9. doi: 10.1056/NEJMoa052256.
2. Butler J, Yang M, Manzi MA, Hess GP, Patel MJ, Rhodes T, et al. Clinical Course of Patients with Worsening Heart Failure with Reduced Ejection Fraction. J Am Coll Cardiol. 2019;73(8):935-44. doi: 10.1016/j.jacc.2018.11.049.
3. Comín-Colet J, Manito N, Segovia-Cubero J, Delgado J, García Pinilla JM, Almenar L, et al. Efficacy and Safety of Intermittent Intravenous Outpatient Administration of Levosimendan in Patients with Advanced Heart Failure: The LION-HEART Multicentre Randomised Trial. Eur J Heart Fail. 2018;20(7):1128-36. doi: 10.1002/ejhf.1145.
4. Psotka MA, Gottlieb SS, Francis GS, Allen LA, Teerlink JR, Adams KF Jr, et al. Cardiac Calcitropes, Myotropes, and Mitotropes: JACC Review Topic of the Week. J Am Coll Cardiol. 2019;73(18):2345-53. doi: 10.1016/j.jacc.2019.02.051.
5. Teerlink JR, Felker GM, McMurray JJ, Solomon SD, Adams KF Jr, Cleland JG, et al. Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure (COSMIC-HF): A Phase 2, Pharmacokinetic, Randomised, Placebo-Controlled Trial. Lancet. 2016;388(10062):2895-903. doi: 10.1016/S0140-6736(16)32049-9.
6. Teerlink JR, Diaz R, Felker GM, McMurray JJV, Metra M, Solomon SD, et al. Cardiac Myosin Activation with Omecamtiv Mecarbil in Systolic Heart Failure. N Engl J Med. 2021;384(2):105-16. doi: 10.1056/NEJMoa2025797.
7. Teerlink JR, Diaz R, Felker GM, McMurray JJV, Metra M, Solomon SD, et al. Effect of Ejection Fraction on Clinical Outcomes in Patients Treated With Omecamtiv Mecarbil in GALACTIC-HF. J Am Coll Cardiol. 2021 Jul 13;78(2):97-108. doi: 10.1016/j.jacc.2021.04.065.
8. Stasch JP, Pacher P, Evgenov OV. Soluble Guanylate Cyclase as an Emerging Therapeutic Target in Cardiopulmonary Disease. Circulation. 2011;123(20):2263-73. doi: 10.1161/CIRCULATIONAHA.110.981738.
9. Armstrong PW, Roessig L, Patel MJ, Anstrom KJ, Butler J, Voors AA, et al. A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of the Efficacy and Safety of the Oral Soluble Guanylate Cyclase Stimulator: The VICTORIA Trial. JACC Heart Fail. 2018;6(2):96-104. doi: 10.1016/j.jchf.2017.08.013.
10. Gheorghiade M, Greene SJ, Butler J, Filippatos G, Lam CS, Maggioni AP, et al. Effect of Vericiguat, a Soluble Guanylate Cyclase Stimulator, on Natriuretic Peptide Levels in Patients With Worsening Chronic Heart Failure and Reduced Ejection Fraction: The SOCRATES-REDUCED Randomized Trial. JAMA. 2015;314(21):2251-62. doi: 10.1001/jama.2015.15734.
11. Armstrong PW, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J, et al. Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2020;382(20):1883-1893. doi: 10.1056/NEJMoa1915928.
12. Voors AA, Mulder H, Reyes E, Cowie MR, Lassus J, Hernandez AF, et al. Renal Function and the Effects of Vericiguat in Patients with Worsening Heart Failure with Reduced Ejection Fraction: Insights from The VICTORIA (Vericiguat Global Study in Subjects with HFrEF) Trial. Eur J Heart Fail. 2021;23(8):1313-21. doi: 10.1002/ejhf.2221.
13. Pieske B, Maggioni AP, Lam CSP, Pieske-Kraigher E, Filippatos G, Butler J, et al. Vericiguat in Patients with Worsening Chronic Heart Failure and Preserved Ejection Fraction: Results of the SOluble guanylate Cyclase stimulatoR in heArT failurE patientS with PRESERVED EF (SOCRATES-PRESERVED) Study. Eur Heart J. 2017;38(15):1119-27. doi: 10.1093/eurheartj/ehw593.
14. Armstrong PW, Lam CSP, Anstrom KJ, Ezekowitz J, Hernandez AF, O'Connor CM, et al. Effect of Vericiguat vs Placebo on Quality of Life in Patients with Heart Failure and Preserved Ejection Fraction: The VITALITY-HFpEF Randomized Clinical Trial. JAMA. 2020;324(15):1512-21. doi: 10.1001/jama.2020.15922.

Review Article

Essential Therapy for Heart Failure with Preserved Ejection Fraction in 2022

Luiz Cláudio Danzmann,[1,2] Joana Carolina Junqueira de Brum,[1,2,3] Leticia Kunst,[1] Priscila Braun,[1] Eduardo Lima Garcia[4]

Universidade Luterana do Brasil (ULBRA),[1] Canoas, RS – Brazil

Santa Casa de Misericórdia,[2] Porto Alegre, RS – Brazil

Hospital São Lucas da PUC-RS,[3] Porto Alegre, RS – Brazil

Hospital de Clínicas de Porto Alegre – Ambulatório de cirurgia cardiovascular,[4] Porto Alegre, RS – Brazil

Abstract

Heart failure with preserved ejection fraction (HFpEF) is a syndrome in which there is clinical evidence of heart failure (HF), left ventricle ejection fraction (LVEF) ≥50%, and evidence of diastolic dysfunction and/or structural cardiac changes. The pathophysiology of HF with preserved LVEF is related to the primary morbidities responsible for cardiac and vascular aggression via a chronic proinflammatory state involving the endothelium. Currently, the foundation of management of HFpEF rests on 5 pillars: control of circulatory congestion, management of primary morbidities or etiologies, use of medications with proven clinical benefit, identification and management of secondary etiologies, and cardiopulmonary rehabilitation. Essential therapy for HFpEF is founded on precise diagnosis, definition of etiology, estimation of severity, and use of medications with cardiovascular action of proven efficacy.

Introduction

Heart failure with preserved ejection fraction (HFpEF) is a complex and heterogeneous clinical syndrome, in which affected populations have a diverse range of phenotypes, frequently associated with multiple comorbidities, and which, in summary, can be diagnosed in the presence of clinical evidence of heart failure (HF), left ventricle ejection fraction (LVEF) ≥50%, and evidence of diastolic dysfunction and/or structural cardiac changes.[1,2] In the vast majority of cases, effective interventions are targeted on the basis of the combination of phenotypes and morbidities present, since there are not yet any treatments that reduce adverse clinical outcomes as effectively as those available for HF with reduced LVEF.[2] The primary explanation for this phenomenon lies in the type of cardiovascular aggression involved, which in HFpEF is caused by the primary morbidities that are responsible for cardiac and, most importantly, vascular aggression, namely: diabetes, hypertension, obesity, chronic kidney disease, chronic obstructive pulmonary disease (COPD), and anemia/iron deficiency. These diseases impose a chronic proinflammatory state that affects the endothelium, reducing nitric oxide bioavailability. This effect is associated with reduced protein kinase G activity in cardiomyocytes with consequent reduction of muscle elasticity, stimulating hypertrophy of these cells. In parallel, vascular cell adhesion molecules and E-selectin provoke interstitial migration of monocytes which are converted into fibroblasts and deposit collagen in the interstitial space, worsening the myocardium's diastolic properties.[3] The result of this process is an absence of myocyte necrosis and, therefore, no, or minimal, systolic dysfunction (figure 1). In this scenario, stimulation of the sympathetic nervous system and renin-angiotensin-aldosterone is much less important than in heart failure with reduced ejection fraction (HFrEF), which partially explains the reduced efficacy of medications that modulate these systems in studies undertaken in populations with HFpEF.

Keywords

Heart Failure; Stroke Volume; Functional Residual Capacity.

Mailing Address: Luiz Cláudio Danzmann •
Rua Gonçalves Dias, 319/804. Postal Code 90130-61, Menino Deus, Porto Alegre, RS – Brazil
E-mail: luiz.danzmann@gmail.com
Manuscript received January 31, 2022, revised manuscript February 01, 2022, accepted February 14, 2022

DOI: https://doi.org/10.36660/abchf.20220011

Essential therapy

Management of HFpEF is based on: 1- control of circulatory congestion with diuretics; 2- management of the primary morbidities or etiologies of the syndrome; 3- specific medications that have recently demonstrated clinical benefits; 4- identification and management of secondary etiologies, such as myocardiopathies, which can even provoke advanced states of HF;[4] and 5- cardiopulmonary rehabilitation.

Control of circulatory congestion

Conventional studies comparing diuretics with placebo in congested patients with HFpEF are ruled out by bioethical considerations, for obvious reasons, but occult and variable congestion is common among these patients and other models of investigation provide evidence that is useful for designing management strategies. The Hong Kong study[5] tested quality of life, functional capacity, and cardiac function indices in a population of 150 participants with New York Heart Association (NYHA) class II-IV HF and LVEF>45% before and after treatment with diuretics (furosemide or thiazide) in isolation or associated with angiotensin converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB) in a model without comparison with placebo. After 12 months of follow-up, use of the diuretic in isolation reduced the symptoms of

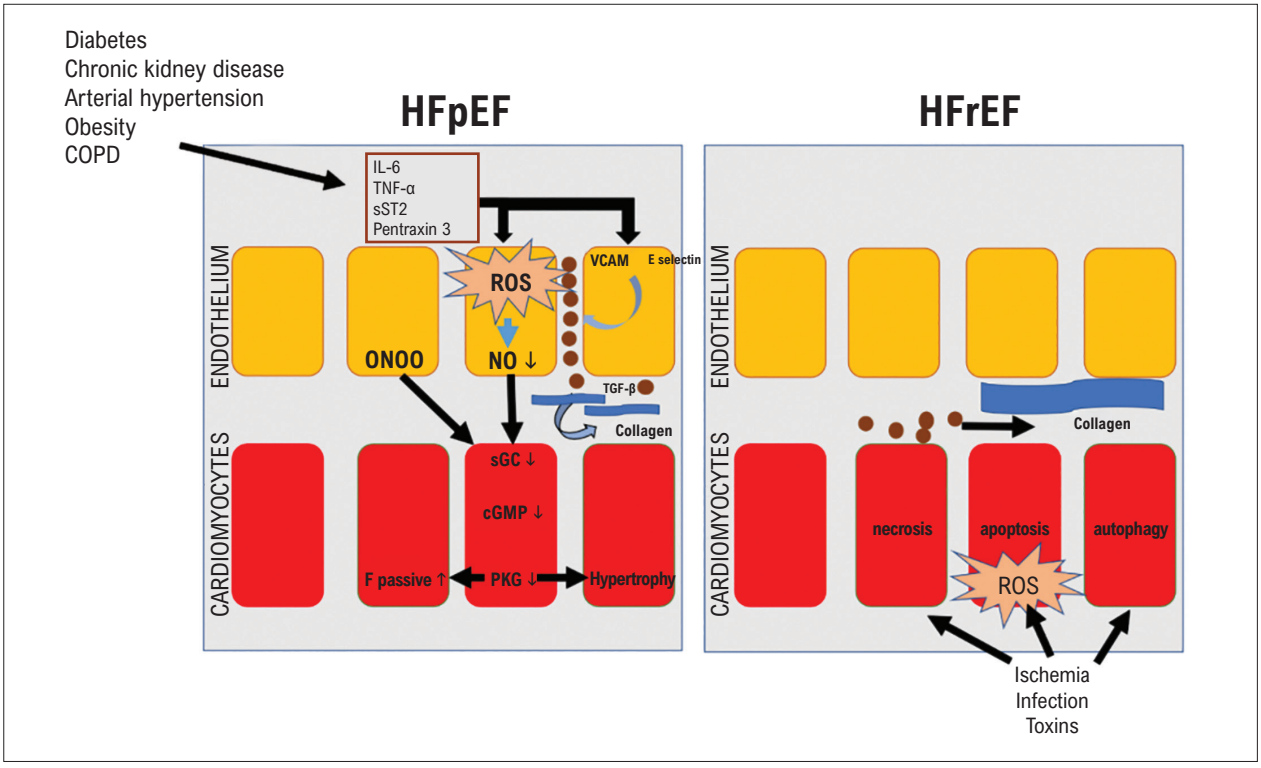


Figure 1 – *Pathophysiology of heart failure according to left ventricle ejection fraction. cGMP: cyclic guanosine monophosphate; COPD: chronic obstructive pulmonary disease; Fpassive: resting tension; IL-6: interleukin 6; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; NO: nitric oxide; ONOO: peroxynitrite; PKG: protein kinase G; sCG: soluble guanylate cyclase; sST2: soluble ST2; TNF: tumor necrosis factor; VCAM: vascular cell adhesion molecule; ROS: oxidative stress; TGF-β: transforming growth factor β. Adapted from Paulus et al.*[3]

HF and improved quality of life (QoL). The association with ACEi or ARB did not result in any additional clinical benefit.

Also focused on the variable pattern of hypervolemia in HFpEF, CardioMEMS is sensor that can be implanted in the pulmonary artery to monitor pulmonary artery blood pressure, offering a potential guide for diuretic therapy. Analysis of data from the CHAMPION study with 119 patients with HFpEF (LVEF ≥40%, ≈50.6%) revealed a 46% reduction in HF-related hospitalizations in 6 months when compared with a traditionally-managed group, with no impact on mortality. Recently, the randomized study GUIDE-HF[7] tested management of HF patients guided by pulmonary artery pressure. The outcomes mortality or HF events (hospital admissions or unplanned emergency visits because of HF) over 12 months were no different in the intervention group. However analysis of the pre-COVID-19 pandemic results demonstrated reductions in primary outcomes, primarily driven by the low rate of hospital admissions (28% reduction in relative risk, p = 0.007). Around 30% of the patients in the study had HFpEF and the reduction in primary outcomes remained consistent even when patients with EF ≥ 50% were analyzed, making the findings consistent with those of the CHAMPION trial.[6] Among other results, these findings provide the foundation for the class I recommendation with evidence level B for diuretic therapy for HFpEF associated with clinical congestion that is contained in the recently published 2021 Updated Brazilian Heart Failure Guidelines.[4]

Management of comorbidities

Control of obesity, hypertension, diabetes, myocardial ischemia, arrhythmia, and peripheral arterial disease has the potential actions of reducing pathophysiologic feedback and improving quality of life and functional capacity. The Brazilian Guidelines for Chronic and Acute HF, from 2018,[8] rate management of morbidities as recommendation class I and evidence level C.

Medications for reduction of robust HF outcomes

There is a discrepancy between the LVEF cutoff point that medical societies use for diagnosis of HFpEF (≥50%) and those used in the designs of randomized clinical trials (RCT) that test the efficacy of drugs for this syndrome. The majority of RCTs allocate participants with LVEF exceeding 40 or 45%, i.e., they are grouped together with an HF population with mildly reduced ejection fraction (HFmrEF), which constitutes a challenge for interpretation and potential extrapolation of the results. Regardless, the drugs for which RCTs had the most appropriate designs were sodium-glucose cotransporter 2 inhibitors (SGLT2i); sacubitril/valsartan; sprinolactone; and, to a lesser extent, angiotensin II receptor blockers (Figure 2) (Table 1).

Sodium-glucose cotransporter 2 inhibitors (SGLT2i)

This drug class has multiple and systemic effects that address several crucial points in the pathophysiology of HFpEF, with

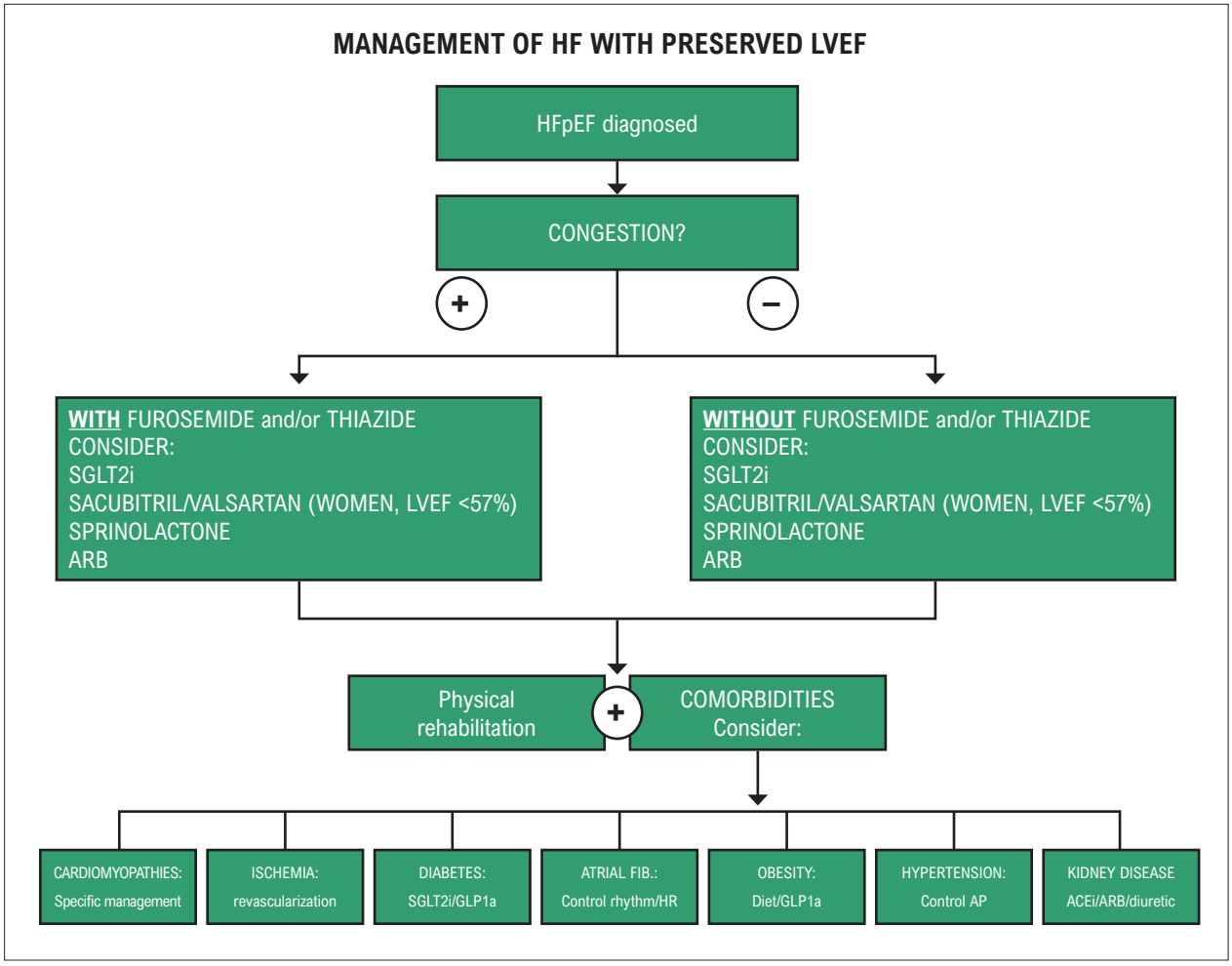


Figure 2 – *Flow diagram of management of HFpEF. ARB: angiotensin II receptor blockers; SGLT2i: sodium-glucose cotransporter 2 inhibitors; Sac-Valsartan: sacubitril-valsartan; LP1a: glucagon-like peptide 1 agonists; Atrial Fib.: atrial fibrillation; AP: atrial pressure; ACEi: angiotensin converting enzyme inhibitors.*

the following potential mechanisms: improved arterial blood pressure; increased natriuresis; improved cellular energy in cardiomyocytes; prevention of inflammation; reduced body weight; improved glucose control; prevention of myocardial remodeling; prevention of ischemia/reperfusion cellular injury; inhibition of the sympathetic nervous system; inhibition of Na+/H+ channels; reduction of hyperuricemia; reduction of epicardial fat; increased serum erythropoietin levels; reduced oxidative stress; improved vascular function; and preserved glomerular function, among others.[9]

Of investigations testing SGLT2i for populations with HFpEF, the SOLOIST-WHF RCT[10] was designed to determine the efficacy of sotagliflozin, an $SGLT_1$ and $SGLT_2$ inhibitor to test the benefit of the drug for the composite outcome primary cardiovascular mortality and/or hospital admissions/urgent visits for HF. Only patients with type 2 diabetes, a diagnosis of HFrEF or HFpEF, and either a recent admission for HF or a need for IV diuretics for exacerbated HF were enrolled. The group allocated to receive the drug exhibited a significant reduction in the primary outcome, both in patients with reduced LVEF and in those with preserved EF (RR=0.67 (95% CI, 0.52–0.85, p<0.001). These results were important and, even though the drug was tested in a specific population of diabetics with recent decompensated HF and follow-up was interrupted prematurely, the effect size of the intervention was striking and statistically significant.

The PRESERVED HF[11] study was a small RCT that tested the efficacy of 10mg of dapagliflozin for 12 weeks for improving quality of life and the functional capacity of the participants with New York Heart Association (NYHA) functional class II, III, and IV HF and LVEF≥45%. The results demonstrated that dapagliflozin improved the Kansas City Cardiomyopathy Questionnaire – Clinical Score (KCCQ-CS) by 5.8 points (95%CI 2.3-9.2, p = 0.001), which was the predefined primary outcome measure. Dapagliflozin also improved performance on the 6-minute walk test (mean effect size was 20.1 meters [95%CI 5.6-34.7, p = 0.007]). It is important to consider that this improvement in KCCQ-CS score was of a higher magnitude than other drugs previously tested for QoL in HF had achieved.

Table 1 – Primary outcomes in phase III randomized clinical trials with cardiovascular outcomes in patients with HFPEF

Study/ Year of publication	Drug	Patients (n)	LVEF (%)	Outcome	Treatment effect, RR (95%CI)
ACEI/ARB					
CHARM- Preserved (2003)	Candesartan vs. Placebo	3023	> 40	Primary: composite of CV mortality or hospital admissions for HF	No difference in primary outcome or all causes mortality
MRA					
TOPCAT (2014)	Sprinolactone vs. Placebo	3445	≥ 45	Primary: composite of CV mortality or hospital admissions for HF	Women: 0.89 (0.71-1.12) Men: 0.89 (0.73-1.09)
TOPCAT- Americas (2014)	Sprinolactone vs. Placebo	1767	≥ 45	Primary: composite of CV mortality or hospital admissions for HF	Women: 0.81 (0.63-1.05) Men: 0.85 (0.67-1.08)
ARNI					
PARAGON (2019)	Sacubitril Valsartan vs. Valsartan	4882	≥ 45	Primary: composite of CV mortality and total hospital admissions for HF	Women: 0.73 (0.59-0.90) Men: 1.03 (0.84-1.25)
SGLT2i					
EMPEROR-PRESERVED (2021)	Empaglifozin vs. Placebo	5988	> 40	Primary: composite of CV mortality and first hospital admissions for HF	Women: 0.75 (0.61-0.92) Men: 0.81 (0.69-0.96)
SOLOIST- WHF (2021)	Sotaglifozin vs. Placebo	1222	All	Primary: composite of CV mortality, hospital admissions for HF, and urgent consultations for HF	Women: 0.80 (0.51-1.25) Men: 0.62 (0.47-0.82)

ARNI: Angiotensin receptor-neprilysin inhibitor; ARB: Angiotensin receptor blocker; CV: Cardiovascular; EMPEROR-Preserved,: Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction; LVEF: Left ventricle ejection fraction; RR: relative risk; HF: heart failure; HFPEF: Heart failure with preserved ejection fraction; ACEI: angiotensin-converting enzyme inhibitor; MRA: mineralocorticoid receptor antagonist; PARAGON: Prospective Comparison of ARNI With ARB on Global Outcomes in HFpEF; SGLT2i: sodium-glucose cotransporter 2 inhibitor; SOLOIST-WHF: Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure; TOPCAT: Treatment of Preserved Cardiac Function HF With an Aldosterone Antagonist.

Empagliflozin is one of the drugs in the class that has been most investigated to date and it was tested at a dosage of 10mg per day against placebo in the EMPEROR Preserved RCT.[12] The study randomized 5988 participants with signs and symptoms of HF, with a HFmrEF + HFpEF profile (LVEF>40%) and elevated serum natriuretic peptides levels. The composite primary outcome was cardiovascular mortality (CV) and/or hospital admissions for HF and secondary outcomes were hospital admissions for HF and progression of decline in glomerular filtration rate (GFR) over the course of the study follow-up period. The population was balanced in terms of sex (55% male), predominantly Caucasian (76%), hypertense (90%), and 49% diabetic. The study's main finding was a 21% reduction in the relative risk of the composite primary outcome (RR=0.79 [95%CI 0.69–0.90], p < 0.001). There was a 29% reduction in the secondary outcome of hospital admissions for HF (RR=0.71 [95%CI: 0.60–0.83], p < 0.001) and the mean progressive decline in GFR was lower in the empagliflozin group (−1.25ml/min/1.73m^2 x -2.62 ml/min/1.73m^2, p < 0.001). The pre-specified analysis of primary outcome results by LVEF strata detected larger effect sizes from the drug in lower LVEF strata, but did not technically demonstrate a difference in interaction between groups that was significant from a statistical point of view (LVEF<50% RR=0.71 [95%CI 0.57–0.88], LVEF≥50%-<60%, RR= 0.80 [95%CI 0.64–0.99], LVEF≥60% RR=0.87 [95%CI 0.69–1.10], P for the interaction was NS). With regard to safety, a higher rate of genital and urinary tract infection and more episodes of uncomplicated hypotension were observed in the empagliflozin group. Publication of this study was a watershed moment for knowledge about HFpEF, since it was the first to demonstrate the efficacy of a drug for reduction of the classic primary outcomes of HF in patients with > 40% LVEF and, although additional data are awaited from ongoing investigations with other SGLT2i, these results have disruptive potential with regard to management of the syndrome.

Sacubitril-valsartan

The sacubitril-valsartan molecule is an inhibitor of both angiotensin and neprilysin that encompasses molecular portions of the neprilysin (neutral endopeptidase) inhibiting pro-drug AHU377 and the ARB valsartan in a single complex. AHU377 is metabolized by enzymatic cleavage into LBQ657, the active neprilysin inhibitor. Neprilysin degrades biologically active natriuretic peptides, including atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and C-type natriuretic peptide, but not

the biologically inert NT-proBNP, which is not a substrate for this enzyme. By increasing active natriuretic peptide, neprilysin inhibition increases generation of myocardial cyclic guanosine 3',5'-monophosphate, which improves myocardial relaxation and reduces hypertrophy. Natriuretic peptides also stimulate diuresis, natriuresis, and vasodilation and may have an additional anti-fibrotic effect and anti-sympathetic effects. However, neprilysin also contributes to degradation of angiotensin, which is the reason for the complex's double action, inhibiting this enzyme and blocking angiotensin activity or generation.[13] The functions performed by this molecule therefore act to partially antagonize the pathophysiologic components of HFpEF mentioned above, provoking natriuresis, vasodilation, and improved myocardial relaxation. In the mechanistic HFmrEF model, blocking angiotensin II provokes vasodilation, reduces stimulation of the sympathetic system, and has anti myocardial fibrosis potential.

The PARAGON-HF study[10] allocated 4822 participants aged ≥50 years, with NYHA HF functional class from II to IV, LVEF≥45%, elevated natriuretic peptide levels, and structural cardiac disease to take either sacubitril-valsartan (target dose of 97 mg of sacubitril with 103 mg of valsartan twice a day) or valsartan (target dose of 160 mg twice a day). The primary outcome was the classic endpoint for HF studies: a composite of hospitalizations for HF and CV mortality. Secondary outcomes were: change in NYHA class; deterioration of renal function, and changes on the Kansas City cardiomyopathy questionnaire (KCCQ) for symptoms and physical limitations. Exclusion criteria were history of LVEF <40%; myocardial infarction, myocardial revascularization surgery, or any event within the 6 months prior to screening; acute decompensated HF requiring treatment; need for treatment with two or more of the following: ACEI, ARB, or renin inhibitor; systolic blood pressure (SBP) <110 mmHg or SBP>180 mmHg at screening; serum potassium >5.2 mmol/L at screening or >5.4 mmol/L at the end of each run-in period; GFR<30 mL/min/1.73m^2 at screening or at the end of each run-in period, GFR <25 mL/min/1.73m^2 or >35% reduction in GFR compared to GFR at screening.

The study design employed the run-in screening model, by which all patients were given valsartan for the first time at half of the target dose, followed by sacubitril-valsartan at half of the target dose in order to only enroll participants who did not have any unacceptable side effects in either run-in phase. Subgroups of the total population were prespecified for the final analysis. The results did not demonstrate statistical significance for reduction of the primary outcome when the entire population of the trial was analyzed (RR: 0.87; 95%CI 0.75 - 1.01, p = 0.06). With regard to the secondary outcomes, NYHA class improved in 15.0% of the patients in the sacubitril-valsartan group and in 12.6% of those in the valsartan group (RR: 1.45; 95%CI, 1.13-1.86); renal function worsened in 1.4% and 2.7%, respectively (RR: 0.50; 95%CI, 0.33 to 0.77). In terms of safety, statistically significant adverse effects were: episodes of systolic pressure < 90 mmHg (2.7% x 1.4%, p<0.001) and angioedema ([0.6 x 0.2] p=0.02). With regard to the 12 prespecified subsets, the sacubitril-valsartan arm had significant benefits for reduction of the primary outcome in participants with LVEF≤ median (57%) (RR:0.78 [95%CI 0.64−0.95]) and females (RR:0.73 [95%CI 0.59-0.90]). On the basis that the benefit of sacubitril-valsartan for patients with LVEF equal to or less than the median is biologically plausible, since several post-hoc analyses of RCTs[14,15] had already shown that drugs classically prescribed for HFrEF, such as sprinolactone and candesartan, had efficacy in patients with HF and LVEF of 40 to 55%, populations that have discrete impairment of systolic function and share mechanisms with populations with preserved LVEF, who are at greater risk of hospital admissions for heart failure, the regulatory agencies ANVISA (National Agency for Sanitary Vigilance [Agência Nacional de Vigilância Sanitária]) in Brazil and FDA (Food and Drug Administration) in the United States approved sacubitril-valsartan for use in patients with HF and LVEF below normal.

Mineralocorticoid receptor antagonists

The largest and most important study to test mineralocorticoid receptor antagonists (MRA) was the *TOPCAT* trial.[16] This RCT randomized 3445 participants with symptoms and signs of HF and LVEF ≥45%, with endogenous creatinine clearance rate >30ml/Kg and serum potassium <5mEq/l, to test sprinolactone vs. placebo. One relevant feature of the study design was the additional eligibility criterion of either a hospital admission for HF or elevation of BNP≥100pg/mL/Nt pro-BNP≥ 360pg/mL. The overall result of the trial was negative for the primary outcome (RR 0.89 [95%CI 0.77–1.04], p= 0.14), but the rate of hospital admissions for HF was 17% lower in the sprinolactone group (RR 0.83 [95%CI 0.69–0.99], p= 0.04). A post-hoc analysis[17] analyzing the efficacy of the drug among participants allocated from the Americas, who had a more congested profile (with eligibility criterion predominantly on the basis of elevated natriuretic peptides) and who also had more events along the time line of the investigation, found an 18% reduction in the primary outcome in the intervention group (RR:0.82 [95%CI 0.69–0.98] p=0.026), contextualizing the potentially better performance of the drug in more hypervolemic patients. The data described above support the current class IIa recommendation in the Brazilian HF Guidelines, since 2018,[8] for sprinolactone for patients with HFpEF, with the main objective of reducing rates of hospital admissions for HF.

Angiotensin II receptor blockers

Angiotensin II receptor blockers are an option for treatment of HFpEF primarily in scenarios in which hypertension is combined with congestion. The best RCT evidence for this drug class is from the CHARM-Preserved study.[18] This trial enrolled 3025 participants with signs and symptoms of HF, NYHA functional class II to IV, and LVEF>40%, but without a need for an objective element of congestion, such as serum natriuretic peptides levels. Candesartan was tested with a target dose of 32mg per day vs. placebo. Approximately 60% of the final sample comprised patients with NYHA class II and around 65% had hypertension. The primary outcome of CV mortality and/or hospital admissions for HF was not different

between the groups (RR: 0.89 [95%CI 0.77-1.03], p=0.118). The secondary outcome of number of individuals with at least one hospital admission for HF was lower in the candesartan group than in the placebo group (230 vs. 279; p=0.017) and the total number of admissions for HF followed the same pattern (402 x 566, p=0.014). In summary, this study provides the only evidence of positive results for ARB in patients with HFmrEF + HFpEF (LVEF>40%). Since 2018, the Brazilian HF Guidelines[8] have given it a IIb recommendation for reduction of hospital admissions in patients with ICFE.

Medications without proven efficacy in clinical trials

RCTs that tested beta blockers; calcium blockers; cardiac glycosides; phosphodiesterase-5 inhibitors; ivabradine; vericiguat; and isosorbide were unable to prove benefit in terms of the outcomes CV mortality or hospital admissions for HF in populations with HFpEF. Currently, they are considered reasonable pharmacological options if prescribed for specific morbidities that cause or are associated with HF.[19]

Management of advanced HFpEF

An advanced heart failure consensus[20] was recently published by the Heart Failure Association (HFA) and European Society of Cardiology (ESC) recognizing that not only patients with HFREF have advanced HF, widening the perspective on treatment and severity of HFPEF, providing that patients meet the criteria for disease severity. In this context, early recognition and referral of these patients is of fundamental importance, since more in-depth assessments and more advanced treatments, such as implantable devices, ventricular assist devices, and heart transplantation can be offered to this patient population in selected cases.

Hypervolemia appears to be the central pathophysiologic mechanism in patients with HFPEF without secondary causes and treatment of the symptoms of HFPEF prioritizes use of diuretics,[21] which has already been covered in this article. Management of congestion in patients with advanced HFPEF can be challenging in certain situations because of the diversity of pathophysiologic mechanisms and comorbidities involved. In patients with uncontrolled arterial hypertension, concomitant vasodilation with blood volume adjustment should be performed with caution, primarily in patients with decompensated HFPEF, since sodium nitroprusside can trigger a more accentuated response in arterial blood pressure drop and systolic volume depression.[22] In hypervolemia cases that are refractory to drug treatment, ultrafiltration should be considered as a useful resource.

Pulmonary hypertension (PH) is a prevalent condition in HFPEF, associated with disease severity and chronicity and worse prognosis.[23] Presence of PH can vary considerably between different phenotypes and may be influenced by the different stages of HFPEF severity, denoting the importance of invasive hemodynamic assessment in this population. We can classify PH according to increase in mean pulmonary artery pressure ≥ 20mmHg, which can be classified a pre-capillary PH, post-capillary PH, or combined PH.[24] This categorization is important, since patients with HFPEF with combined PH may benefit from treatment with pulmonary vasodilators.[25] Assessments of the contractile function of the right ventricle and of the PH of patients with advanced HF are of fundamental importance. Assessment with direct cardiac catheterization at rest and during exercise, when indicated, yields more trustworthy parameters of right ventricular function and PH. Even in advanced HF, we may see normal right ventricular function at rest, but then abnormal under exercise if the dilatation capacity of the pulmonary vasculature is lost in response to the increase in volume. Under normal conditions, the right ventricle is less resistant to changes in afterload and this mechanism is exacerbated in individuals with HFpEF.[26,27] Use of inotropics in decompensated HFPEF is still a gray area, with only small studies in patients with associated PH, and should be reserved for selected cases.[28] Use of levosimendan in these patients is being tested in an ongoing randomized study, the HELP RCT (NCT 03541603), which should provide further explanations.

Treatments targeting PH with the aim of reducing right ventricle afterload have so far yielded disappointing results. In a small, randomized, double-blind study with 44 patients, sildenafil was associated with improvement in pulmonary pressure, right ventricular function, left ventricular relaxation, and pulmonary hydrostatic balance.[29] Although the drug exhibited good tolerability, later randomized studies did not report the same findings, with positive results only reported by one observational study with no control group, which observed improvements in NYHA HF, TC6M, and NT-proBNP levels at 3 and 12 months in patients with combined PH.[30] Ongoing studies in this population, such as DYNAMIC (NCT02744339) which is investigating riociguat, SERENADE (NCT03153111), testing macitentan, and the VITALITY-HFpEF RCT (NCT03547583), which will assess vericiguat, will provide more answers. Long-stay ventricular assist devices (VAD) are part of the therapeutic arsenal for treatment of patients with advanced HF in patients with HFrEF, demonstrating improved morbidity and mortality statistics.[31] However, there are few studies reporting data on VADs implanted in patients with HFPEF, in the majority of cases in patients with hypertrophic and restrictive cardiomyopathy.[32-35] This is because of the peculiar and pathophysiologic characteristic of these patients, the majority of whom have increased myocardial rigidity, altered complacency and, in some situations, small left ventricular dimensions. These characteristics may favor complications linked to VAD, such as obstructions of cannulae, suction events, inadequate pump flow, and pump thrombosis.[33,36] An additional myectomy at the time that the VAD is implanted may be a viable option, as has been performed in some cases of hypertrophic cardiomyopathy.[33]

A small proportion of patients with HFPEF meet the criteria for heart transplantation, although published data are scant. In this population, hypertrophic and restrictive cardiomyopathies and selected cases of right ventricular dysfunction stand out. For individuals with severely symptomatic hypertrophic cardiomyopathy (NYHA III-IV HF) with EF ≥ 50% (without obstruction of the LV outlet) and with impaired cardiopulmonary exercise testing results, with peak VO_2 ≤ 14 ml/mun/Kg or ≤ 50% of predicted, unfavorable hemodynamic profile, or acute hemodynamic deterioration, consideration of heart transplantation appears to be beneficial,

with favorable post-transplant outcomes. In restrictive cardiomyopathies, after ruling out constrictive pericarditis, it is mandatory to conduct etiological assessment for adequate treatment of the underlying condition (amyloidosis, Anderson-Fabry, sarcoidosis, etc.) and assessment of involvement of other organs (amyloidosis, hemochromatosis) and it may even be necessary to plan post-transplant treatment, with a need for double transplant in some situations.[37]

Advanced treatments such as long-stay circulatory support and heart transplantation are applicable and more consolidated for HFPEF of secondary etiology, such as hypertrophic and restrictive cardiomyopathies. This is why it always essential to identify the etiology.

Cardiopulmonary rehabilitation in HFpEF

In this group, exercise intolerance may be because of remodeling and ventricular rigidity, causing impairment of the Frank-Starling mechanism, which, associated with chronotropic deficit, are determinants of failure to raise cardiac output, thereby reducing maximum oxygen uptake. Garcia et al,[38] observed the dynamics of patients with HFPEF vs. controls and identified lower oxygen consumption (VO_2) and reduced capacity to reduce heart rate after effort and this was associated with atrial remodeling and elevation of the estimated diastolic pressure of the LV. As a result, rehabilitation focused on aerobic activity has been tested with these patients. In a recent systematic review, Pandey, et al.,[39] demonstrated that patients with HFpEF who enrolled on a cardiac rehabilitation program improved their cardiorespiratory fitness (2ml/kg/min), quality of life (by seven points), and diastolic function after 12 weeks of intervention. Although there is no evidence of CV mortality reductions with exercise in this population, Kavanagh, et al.[40] have demonstrated that for each 1ml/kg/min unit increase in oxygen consumption, cardiovascular mortality drops by 10%.

Alternative rehabilitation methods such as training of inspiratory musculature are already in use. Menezes MG, et al.[41] demonstrated that one acute session of high intensity inspiratory muscles training (80% of the maximum inspiratory effort) improved late arterial rigidity (60 min after the assessment) and diastolic function indices. Supplementing this from a practical point of view, Palau et al.[42] allocated a sample of 26 patients with HFPEF to a program of 12 weeks' inspiratory muscle training at 30% of maximum inspiratory effort or usual treatment, observing a significant improvement in maximum inspiratory pressure ($p < 0.001$), peak VO_2 ($p < 0.001$), oxygen consumption during exercise at the anaerobic threshold ($p = 0.001$), ventilatory efficiency ($p = 0.007$), metabolic equivalents ($p < 0.001$), and the 6-minute walk test ($p < 0.001$), in comparison to the control group.

Prospects for management of HFpEF

The future of treatment of HFpEF lies in studies with designs that are more compatible with the real population, possibly with higher LVEF cutoff points, and respecting phenotypical characteristics, and in investing in molecules with activity on fibrosis, inflammation, improvement of mitochondrial function, anti-remodeling, optimizers of endothelial function, and in devices to regulate circulatory overload.

Conclusions

Essential therapy for HFpEF is intimately related to precise diagnosis, definition of etiology, and estimation of severity, and use of medications with cardiovascular action of proven efficacy. After this first step, treatment of morbidities, rational use of diuretic therapy, and physical training for stable patients is the foundation of management. Finally, use of drugs with cardiovascular activity of proven efficacy can benefit clinical outcomes, when well-chosen.

Author Contributions

Conception and design of the research: Danzmann LC, Brum JCJ, Braun P; Acquisition of data: Danzmann LC, Brum JCJ, Kunst L, Braun P; Analysis and interpretation of the data, Statistical analysis and Critical revision of the manuscript for intellectual contente: Danzmann LC; Obtaining financing: Danzmann LC, Brum JCJ; Writing of the manuscript: Danzmann LC, Brum JCJ, Kunst L, Garcia EL.

Potential Conflict of Interest

Dr. Luiz Cláudio Danzmann - speaker: Novartis, Astra Zeneca, Boehringer e Lilly.

Dra. Joana Carolina Junqueira de Brum - speaker: Novartis.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Danzmann LC, Belyavskiy E, Jorge AJL, Mesquita ET, Torres MAR. The Challenge of HFpEF Diagnosis in Brazil. ABC Heart Fail Cardiomyop. 2021;1(1):63-6. doi: 10.36660/abchf.20210011.

2. Shah SJ, Borlaug BA, Kitzman DW, McCulloch AD, Blaxall BC, Agarwal R, et al. Research Priorities for Heart Failure With Preserved Ejection Fraction: National Heart, Lung, and Blood Institute Working Group Summary. Circulation. 2020;141(12):1001-26. doi: 10.1161/CIRCULATIONAHA.119.041886.

3. Paulus WJ, Tschöpe C. A Novel Paradigm for Heart Failure with Preserved Ejection Fraction: Comorbidities Drive Myocardial Dysfunction and Remodeling Through Coronary Microvascular Endothelial Inflammation. J Am Coll Cardiol. 2013;62(4):263-71. doi: 10.1016/j.jacc.2013.02.092.

4. Marcondes-Braga FG, Moura LAZ, Issa VS, Vieira JL, Rohde LE, Simões MV, et al. Emerging Topics Update of the Brazilian Heart Failure Guideline - 2021. Arq Bras Cardiol. 2021;116(6):1174-1212. doi: 10.36660/abc.20210367.

5. Yip GW, Wang M, Wang T, Chan S, Fung JW, Yeung L, et al. The Hong Kong Diastolic Heart Failure Study: A Randomised Controlled Trial of Diuretics, Irbesartan and Ramipril on Quality of Life, Exercise Capacity, Left Ventricular Global and Regional Function in Heart Failure with a Normal Ejection Fraction. Heart. 2008;94(5):573-80. doi: 10.1136/hrt.2007.117978.

6. Adamson PB, Abraham WT, Bourge RC, Costanzo MR, Hasan A, Yadav C, et al. Wireless Pulmonary Artery Pressure Monitoring Guides Management to Reduce Decompensation in Heart Failure with Preserved Ejection Fraction. Circ Heart Fail. 2014;7(6):935-44. doi: 10.1161/CIRCHEARTFAILURE.113.001229.

7. Lindenfeld J, Zile MR, Desai AS, Bhatt K, Ducharme A, Horstmanshof D, et al. Haemodynamic-guided Management of Heart Failure (GUIDE-HF): A Randomised Controlled Trial. Lancet. 2021;398(10304):991-1001. doi: 10.1016/S0140-6736(21)01754-2.

8. Rohde LEP, Montera MW, Bocchi EA, Clausell NO, Albuquerque DC, Rassi S, et al. Diretriz Brasileira de Insuficiência Cardíaca Crônica e Aguda. Arq Bras Cardiol. 2018;111(3):436-539. doi: 10.5935/abc.20180190.

9. Martins CNG, Bau AA, Silva LM, Coelho Filho OR. Possible Mechanisms of Action of SGLT2 Inhibitors in Heart Failure. ABC Heart Fail Cardiomyop. 2021;1(1):33-43. doi: 10.36660/abchf.20210007.

10. Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, et al. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. N Engl J Med. 2021;384(2):117-28. doi: 10.1056/NEJMoa2030183.

11. Nassif ME, Windsor SL, Borlaug BA, Kitzman DW, Shah SJ, Tang F, et al. The SGLT2 Inhibitor Dapagliflozin in Heart Failure with Preserved Ejection Fraction: A Multicenter Randomized Trial. Nat Med. 2021;27(11):1954-60. doi: 10.1038/s41591-021-01536-x.

12. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med. 2021;385(16):1451-61. doi: 10.1056/NEJMoa2107038.

13. Solomon SD, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, et al. The Angiotensin Receptor Neprilysin Inhibitor LCZ696 in Heart Failure with Preserved Ejection Fraction: A Phase 2 Double-blind Randomised Controlled Trial. Lancet. 2012;380(9851):1387-95. doi: 10.1016/S0140-6736(12)61227-6.

14. Solomon SD, Claggett B, Lewis EF, Desai A, Anand I, Sweitzer NK, et al. Influence of Ejection Fraction on Outcomes and Efficacy of Spironolactone in Patients with Heart Failure with Preserved Ejection Fraction. Eur Heart J. 2016;37(5):455-62. doi: 10.1093/eurheartj/ehv464.

15. Lund LH, Claggett B, Liu J, Lam CS, Jhund PS, Rosano GM, et al. Heart Failure with Mid-range Ejection Fraction in CHARM: Characteristics, Outcomes and Effect of Candesartan Across the Entire Ejection Fraction Spectrum. Eur J Heart Fail. 2018;20(8):1230-9. doi: 10.1002/ejhf.1149.

16. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, et al. Spironolactone for Heart Failure with Preserved Ejection Fraction. N Engl J Med. 2014;370(15):1383-92. doi: 10.1056/NEJMoa1313731.

17. Pfeffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N, et al. Regional Variation in Patients and Outcomes in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) Trial. Circulation. 2015;131(1):34-42. doi: 10.1161/CIRCULATIONAHA.114.013255.

18. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, et al. Effects of Candesartan in Patients with Chronic Heart Failure and Preserved Left-ventricular Ejection Fraction: The CHARM-Preserved Trial. Lancet. 2003;362(9386):777-81. doi: 10.1016/S0140-6736(03)14285-7.

19. Gevaert AB, Kataria R, Zannad F, Sauer AJ, Damman K, Sharma K, et al. Heart Failure with Preserved Ejection Fraction: Recent Concepts in Diagnosis, Mechanisms and Management. Heart. 2022:heartjnl-2021-319605. doi: 10.1136/heartjnl-2021-319605.

20. Crespo-Leiro MG, Metra M, Lund LH, Milicic D, Costanzo MR, Filippatos G, et al. Advanced Heart Failure: A Position Statement of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2018;20(11):1505-35. doi: 10.1002/ejhf.1236.

21. Masip J, Peacok WF, Arrigo M, Rossello X, Platz E, Cullen L, et al. Acute Heart Failure in the 2021 ESC Heart Failure Guidelines: A Scientific Statement from the Association for Acute CardioVascular Care (ACVC) of the European Society of Cardiology. Eur Heart J Acute Cardiovasc Care. 2022;11(2):173-85. doi: 10.1093/ehjacc/zuab122.

22. Burke MA, Katz DH, Beussink L, Selvaraj S, Gupta DK, Fox J, et al. Prognostic Importance of Pathophysiologic Markers in Patients with Heart Failure and Preserved Ejection Fraction. Circ Heart Fail. 2014;7(2):288-99. doi: 10.1161/CIRCHEARTFAILURE.113.000854.

23. Lam CS, Roger VL, Rodeheffer RJ, Borlaug BA, Enders FT, Redfield MM. Pulmonary Hypertension in Heart Failure with Preserved Ejection Fraction: A Community-based Study. J Am Coll Cardiol. 2009;53(13):1119-26. doi: 10.1016/j.jacc.2008.11.051.

24. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamic Definitions and Updated Clinical Classification of Pulmonary Hypertension. Eur Respir J. 2019;53(1):1801913. doi: 10.1183/13993003.01913-2018.

25. Hoeper MM, Lam CSP, Vachiery JL, Bauersachs J, Gerges C, Lang IM, et al. Pulmonary Hypertension in Heart Failure with Preserved Ejection Fraction: A Plea for Proper Phenotyping and Further Research. Eur Heart J. 2017;38(38):2869-73. doi: 10.1093/eurheartj/ehw597.

26. Melenovsky V, Hwang SJ, Lin G, Redfield MM, Borlaug BA. Right Heart Dysfunction in Heart Failure with Preserved Ejection Fraction. Eur Heart J. 2014;35(48):3452-62. doi: 10.1093/eurheartj/ehu193.

27. Vonk Noordegraaf A, Westerhof BE, Westerhof N. The Relationship Between the Right Ventricle and its Load in Pulmonary Hypertension. J Am Coll Cardiol. 2017;69(2):236-43. doi: 10.1016/j.jacc.2016.10.047.

28. Kaye DM, Nanayakkara S, Vizi D, Byrne M, Mariani JA. Effects of Milrinone on Rest and Exercise Hemodynamics in Heart Failure with Preserved Ejection Fraction. J Am Coll Cardiol. 2016;67(21):2554-6. doi: 10.1016/j.jacc.2016.03.539.

29. Cheitlin MD. Pulmonary Hypertension in Heart Failure with Preserved Ejection Fraction: A Target of Phosphodiesterase-5 Inhibition in a 1-Year Study. Yearbook of Cardiology. 2012;2012(1):340–2. doi: 10.1016/j.ycar.2012.01.055.

30. Opitz CF, Hoeper MM, Gibbs JS, Kaemmerer H, Pepke-Zaba J, Coghlan JG, et al. Pre-Capillary, Combined, and Post-Capillary Pulmonary Hypertension: A Pathophysiological Continuum. J Am Coll Cardiol. 2016;68(4):368-78. doi: 10.1016/j.jacc.2016.05.047.

31. Kirklin JK, Pagani FD, Kormos RL, Stevenson LW, Blume ED, Myers SL, et al. Eighth Annual INTERMACS Report: Special Focus on Framing the Impact of Adverse Events. J Heart Lung Transplant. 2017;36(10):1080-6. doi: 10.1016/j.healun.2017.07.005.

32. Topilsky Y, Pereira NL, Shah DK, Boilson B, Schirger JA, Kushwaha SS, et al. Left Ventricular Assist Device Therapy in Patients with Restrictive and Hypertrophic Cardiomyopathy. Circ Heart Fail. 2011;4(3):266-75. doi: 10.1161/CIRCHEARTFAILURE.110.959288.

33. Sreenivasan J, Kaul R, Khan MS, Ranka S, Demmer RT, Yuzefpolskaya M, et al. Left Ventricular Assist Device Implantation in Hypertrophic and Restrictive Cardiomyopathy: A Systematic Review. ASAIO J. 2021;67(3):239-44. doi: 10.1097/MAT.0000000000001238.

34. Wynne E, Bergin JD, Ailawadi G, Kern JA, Kennedy JL. Use of a Left Ventricular Assist Device in Hypertrophic Cardiomyopathy. J Card Surg. 2011;26(6):663-5. doi: 10.1111/j.1540-8191.2011.01331.x.

35. Muthiah K, Phan J, Robson D, Macdonald PS, Keogh AM, Kotlyar E, et al. Centrifugal Continuous-flow Left Ventricular Assist Device in Patients with Hypertrophic Cardiomyopathy: A Case Series. ASAIO J. 2013;59(2):183-7. doi: 10.1097/MAT.0b013e318286018d.

36. Rowin EJ, Maron BJ, Kiernan MS, Casey SA, Feldman DS, Hryniewicz KM, et al. Advanced Heart Failure with Preserved Systolic Function in

Nonobstructive Hypertrophic Cardiomyopathy: Under-recognized Subset of Candidates for Heart Transplant. Circ Heart Fail. 2014;7(6):967-75. doi: 10.1161/CIRCHEARTFAILURE.114.001435.

37. Mehra MR, Canter CE, Hannan MM, Semigran MJ, Uber PA, Baran DA, et al. The 2016 International Society for Heart Lung Transplantation Listing Criteria for Heart Transplantation: A 10-year Update. J Heart Lung Transplant. 2016;35(1):1-23. doi: 10.1016/j.healun.2015.10.023.

38. Garcia EL, Menezes MG, Stefani CM, Danzmann LC, Torres MA. Ergospirometry and Echocardiography in Early Stage of Heart Failure with Preserved Ejection Fraction and in Healthy Individuals. Arq Bras Cardiol. 2015;105(3):248-55. doi: 10.5935/abc.20150085.

39. Pandey A, Parashar A, Kumbhani D, Agarwal S, Garg J, Kitzman D, et al. Exercise Training in Patients with Heart Failure and Preserved Ejection Fraction: Meta-analysis of Randomized Control Trials. Circ Heart Fail. 2015;8(1):33-40. doi: 10.1161/CIRCHEARTFAILURE.114.001615.

40. Kavanagh T, Mertens DJ, Hamm LF, Beyene J, Kennedy J, Corey P, et al. Peak Oxygen Intake and Cardiac Mortality in Women Referred for Cardiac Rehabilitation. J Am Coll Cardiol. 2003;42(12):2139-43. doi: 10.1016/j.jacc.2003.07.028.

41. Menezes MG, Garcia EL, Franzoni LT, Grings V, Danzmann LC. Acute Inspiratory Muscle Training Modifies Hemodynamic Indices in Patients with Heart Failure with Preserved Ejection Fraction. Arq Bras Cardiol HF & Cardiomyopathy. 2021; 1(1):27-32. doi: 10.36660/abchf.20210006.

42. Palau P, Domínguez E, Núñez E, Schmid JP, Vergara P, Ramón JM, et al. Effects of Inspiratory Muscle Training in Patients with Heart Failure with Preserved Ejection Fraction. Eur J Prev Cardiol. 2014;21(12):1465-73. doi: 10.1177/2047487313498832.

The EMPEROR-Preserved Trial: Results that Innovate the Treatment of Heart Failure with Preserved Ejection Fraction

Ricardo Mourilhe-Rocha,[1,2] Marcelo Imbroinise Bittencourt,[1,3] Felipe Neves de Albuquerque,[1,4] Ana Luiza Ferreira Salles,[1,2] Pedro Pimenta de Mello Spineti,[1,5] Denilson Campos de Albuquerque[1,6]

Universidade do Estado do Rio de Janeiro,[1] Rio de Janeiro, RJ – Brazil

Hospital Pró-Cardíaco - Américas Serviços Médicos,[2] Rio de Janeiro, RJ – Brazil

Grupo DASA,[3] Centro, RJ – Brazil

Hospital Samaritano Botafogo – Américas Serviços Médicos,[4] Rio de Janeiro, RJ – Brazil

Hospital Unimed Rio,[5] Rio de Janeiro, RJ – Brazil

Instituto D´Or de Pesquisa e Ensino (IDOR),[6] Rio de Janeiro, RJ – Brazil

The treatment of heart failure with reduced ejection fraction (HFrEF) has been improving by numerous pharmacological and non-pharmacological options, as described in national and international guidelines. However, in the scenario of patients with HF with preserved EF (HFpEF), no therapeutic update has occurred since the last published guideline.[1-4]

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are effective hypoglycemic agents in type 2 diabetes mellitus (T2DM) and are associated with improved glycemic control as well as with reduced body mass and blood pressure. In large-scale randomized trials of patients with diabetes, the use of SGLT2 inhibitors has improved cardiovascular and renal outcomes – including hospitalization for HF (HHF). This benefit was also observed in patients without diabetes who have HFrEF.[5] That is, the presence of T2DM is not necessary to endorse the clinical benefit of SGLT2 inhibitors in HFrEF.[5]

Recently, the classification of forms of HF according to EF was redefined, but the definition of EF ≥50% for HFpEF was maintained.[6] This is a crucial point, since the EMPEROR-Preserved trial used an EF cutoff of 40% for patient inclusion – that is, it included patients with EFs 41% to 50% classified as HF with slightly reduced EF.[6] However, the authors were careful to prespecify subgroups according to EF, which allowed the interpretation of specific results for each EF range, thus reinforcing the value of this statistical analysis.[7]

The recently published EMPEROR-Preserved results demonstrate, in an unprecedented way, solid benefits of empagliflozin for patients with HFpEF. It reduced the combined risk of cardiovascular death, HHF, or HF emergency visit. This benefit started at day 18 post-randomization. There was also a reduction in the total number of HHFs (first and recurrent) as well as in hospitalizations for any cause. Advantages were evinced in all HF severity spectra: in the most severe one, there were fewer HHFs in intensive care and less need for vasopressors or positive inotropes. In the outpatient setting, fewer patients on empagliflozin required increased diuretics and there was a higher likelihood (1.2 to 1.5x) of improvement in the New York Heart Association (NYHA) functional class.[7] Despite the consistent effect of reducing HHFs in these scenarios, there was no impact on cardiovascular death alone or on total deaths. Therefore, the combined primary outcome proved to be statistically significant at the expense of the impact on hospitalizations, which does not underestimate the beneficial effect of the drug for HFpEF.[7]

As mentioned earlier, in order to study the impact on different EF ranges, the authors analyzed 3 EF subgroups. The benefit of reducing HHFs was similar across the lower EF ranges (40%-50% and 51%-60%), but it was attenuated in the subgroup with higher EFs (above 60%).[7-10]

Another relevant aspect of the EMPEROR-Preserved trial was the use of the Kansas City Cardiomyopathy Questionnaire (KCCQ) to assess the impact on quality of life (QoL). Two results were prominent. First, the benefit of reducing cardiovascular outcomes was independent of the severity of the symptoms presented at the beginning of the follow-up (ie, with a lower KCCQ score). Second, the mean KCCQ score was better in the intervention group over the 26.2 months of follow-up reflecting a gain in QoL – an effect that appeared early and was maintained for at least 12 months. This advantage was seen in all patients, regardless of their KCCQ or NYHA data at baseline. These findings reinforce the importance of early initiation of empagliflozin in HFpEF.[11,12]

This type of finding is similar to that reported in other randomized trials of HFpEF (such as TOPCAT and PARAGON-HF). It is important to highlight, however, that this impact on QoL was also attenuated in patients with EFs ≥60% to 65% (as well as for HHFs).[11]

In contrast to these favorable effects, empagliflozin did not reproduce this pattern in major renal outcomes – defined as a sustained ≥40% reduction in estimated glomerular filtration rate (renal death was not included in this outcome in the EMPEROR-Preserved trial). These disagreements were intriguing because, in previous clinical trials, the effect of SGLT2 inhibitors on HF and renal outcomes was consistent.[11]

Keywords

Heart Failure; Treatment; Preserved Ejection Fraction.

Mailing Address: Ricardo Mourilhe-Rocha •
Rua Voluntários da Pátria, 445/1402. Postal Code 22270-000, Botafogo, Rio de Janeiro, RJ – Brazil
E-mail: ricardomourilhe@gmail.com
Manuscript received January 21, 2022, revised manuscript February 01, 2022, accepted February 16, 2022

DOI: https://doi.org/10.36660/abchf.20220012

An explanation for the lack of "renal protection" in the EMPEROR-Preserved trial may be the definition of renal outcomes. A meta-analysis demonstrated agreement between the effects of SGLT2 inhibitors on HF and renal outcomes when using a more conventional definition of renal outcomes, a finding in line with observations of the effects of this drug class in other large-scale studies of patients with T2DM.[13]

A perplexing factor in the interpretation of HFpEF studies is the heterogeneity of the EF thresholds adopted to define it. Inclusion criteria were ≥40% in PEP-CHF, >40% in CHARM-Preserved, and ≥45% in I-PRESERVED, TOPCAT, and PARAGON-HF. Note that, as in the EMPEROR-Preserved trial, all patients with slightly reduced EF were included, not just those diagnosed with HFpEF according to the latest universal classification (EF ≥50%). This seems to be a relevant and weak point, as the greatest benefits in the primary outcomes of these studies were recorded for a left ventricular EF of 40% to 50%, whereas the same treatments were ineffective for patients with an EF >60%. The same pattern was observed in the EMPEROR-Preserved subgroup analysis.[14]

When analyzing the characteristics of the EMPEROR-Preserved population, there was a higher percentage of patients with T2DM in the EMPEROR-Preserved trial (49% vs 33% TOPCAT vs 43% PARAGON), which may have contributed to the overall benefits of empagliflozin in addition to standard therapy. Furthermore, only 2% of patients received sacubitril/valsartan, and the combined use of these drugs in the management of HFpEF warrants further investigation.[14]

A comparison of the effects reported in 2 randomized trials of patients with HFpEF evaluating the benefits of neprilysin inhibition and SGLT2 inhibition using the same EF cutoffs in comparable patient populations would be ideal. Currently, we can use indirect comparisons between PARAGON (sacubitril-valsartan) and EMPEROR-Preserved (empagliflozin) to infer which drug provides the greatest clinical benefit in HFpEF. Thus, in the outcomes that include HHF, the effect size appears to be larger for empagliflozin in most EF subgroups. We highlight the odds ratio (OR) of one of these outcomes, time to first HHF, to illustrate these findings in the table below.[15]

The magnitude of the reduction in the risk of serious HF outcomes appears to be greater with SGLT2 inhibition than with neprilysin inhibition for most patients with HFpEF.[15]

Although the EMPEROR-Preserved results may indicate a long-awaited advance in the approach to HFpEF, the heterogeneous patient profile motivates the design of studies based on a more accurate phenotypic characterization. This scenario would allow us to take advantage of the predominant mechanism of action of the different agents available in individually appropriate clinical phenotypes.

Additionally, evidence is still lacking on how to treat patients with EF ≥60%-65%, and we need to wait for the results of other ongoing studies using SGLT2 inhibitors in HFpEF to know how to act in this scenario.

Finally, we can say that we have left ground zero and, in the current context of scientific knowledge, the use of SGLT2 inhibitors in HFpEF seems to be the best therapeutic option for these individuals.

Author Contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data and Writing of the manuscript: Mourilhe-Rocha R; Critical revision of the manuscript for intellectual content: Mourilhe-Rocha R, Albuquerque DC.

Potential Conflict of Interest

Dr. Ricardo Mourilhe-Rocha - advisor and speaker for: Boehringer-Lilly, Astrazeneca, Novartis, Bayer, Servier, Daichi Sankyo, Pfizer, Proadi-SUS.

Dr. Marcelo Imbroinise Bittencourt - advisor and speaker for: Bristol-Myers Squibb e Sanofi Genzyme.

Dr. Felipe Neves de Albuquerque - advisor and speaker for: Novartis e Boehringer-Lilly.

Dr. Pedro Pimenta de Mello Spineti - clinical resarch: Boehringer e Proadi-SUS.

Dr. Denilson Campos de Albuquerque - advisor and speaker for: Boehringer-Lilly, Astrazeneca, Novartis, Bayer, Pfizer.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Table 1 – Odds Ratio for Time to First Hospitalization for Heart Failure: Comparison between PARAGON-HF vs EMPEROR-Preserved according to ejection fraction subgroups

EF subgroup	PARAGON-HF	EMPEROR-Preserved
>42.5% to ≤52.5%	0.83 (0.65-1.06*)	0.65 (0.50-0.85*)
>52.5% to ≤62.5%	0.87 (0.71-1.07*)	0.68 (0.51-0.89*)

*EF: ejection fraction, Odds ratio: Hazard rate, *95% confidence interval*

References

1. Marcondes-Braga FG, Moura LAZ, Issa VS, Vieira JL, Rohde LE, Simões MV, et al. Emerging Topics Update of the Brazilian Heart Failure Guideline - 2021. Arq Bras Cardiol. 2021;116(6):1174-212. doi: 10.36660/abc.20210367.
2. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. Eur Heart J. 2021;42(36):3599-3726. doi: 10.1093/eurheartj/ehab368.
3. Maddox TM, Januzzi JL Jr, Allen LA, Breathett K, Butler J, Davis LL, et al. 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure with Reduced Ejection Fraction: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2021;77(6):772-810. doi: 10.1016/j.jacc.2020.11.022.
4. Fernandes-Silva MM, Mourilhe-Rocha R, Brito FS, Jorge AJL, Issa VS, Danzmann LC. Emerging Topics in Heart Failure: Heart Failure with Preserved and Mid-Range Ejection Fraction. Arq Bras Cardiol. 2020;115(5):949-52. doi: 10.36660/abc.20201105.
5. Cowie MR, Fisher M. SGLT2 Inhibitors: Mechanisms of Cardiovascular Benefit Beyond Glycaemic Control. Nat Rev Cardiol. 2020;17(12):761-72. doi: 10.1038/s41569-020-0406-8.
6. Bozkurt B, Coats AJ, Tsutsui H, Abdelhamid M, Adamopoulos S, Albert N, et al. Universal Definition and Classification of Heart Failure: A Report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. J Card Fail. 2021:S1071-9164(21)00050-6. doi: 10.1016/j.cardfail.2021.01.022.
7. Anker SD, Butler J, Filippatos G, Khan MS, Ferreira JP, Bocchi E, et al. Baseline Characteristics of Patients with Heart Failure with Preserved Ejection Fraction in the EMPEROR-Preserved Trial. Eur J Heart Fail. 2020;22(12):2383-92. doi: 10.1002/ejhf.2064.
8. Anker SD, Butler J, Filippatos GS, Jamal W, Salsali A, Schnee J, et al. Evaluation of the Effects of Sodium-glucose Co-transporter 2 Inhibition with Empagliflozin on Morbidity and Mortality in Patients with Chronic Heart Failure and a Preserved Ejection Fraction: Rationale for and Design of the EMPEROR-Preserved Trial. Eur J Heart Fail. 2019;21(10):1279-87. doi: 10.1002/ejhf.1596.
9. Packer M, Butler J, Zannad F, Filippatos G, Ferreira JP, Pocock SJ, et al. Effect of Empagliflozin on Worsening Heart Failure Events in Patients with Heart Failure and Preserved Ejection Fraction: EMPEROR-Preserved Trial. Circulation. 2021;144(16):1284-94. doi: 10.1161/CIRCULATIONAHA.121.056824.
10. Huynh K. Empagliflozin Improves Clinical Outcomes for HFpEF in EMPEROR-Preserved. Nat Rev Cardiol. 2021;18(11):737. doi: 10.1038/s41569-021-00627-z.
11. Butler J, Filippatos G, Siddiqi TJ, Brueckmann M, Böhm M, Chopra VK, et al. Empagliflozin, Health Status, and Quality of Life in Patients with Heart Failure and Preserved Ejection Fraction: The EMPEROR-Preserved Trial. Circulation. 2022;145(3):184-93. doi: 10.1161/CIRCULATIONAHA.121.057812.
12. Butler J, Siddiqi TJ, Filippatos G, Ferreira JP, Pocock SJ, Zannad F, et al. Early Benefit with Empagliflozin in Heart Failure with Preserved Ejection Fraction: Insights from the EMPEROR-Preserved Trial. Eur J Heart Fail. 2022 [ahead of print]. doi: 10.1002/ejhf.2420.
13. Packer M, Zannad F, Butler J, Filippatos G, Ferreira JP, Pocock SJ, et al. Influence of Endpoint Definitions on the Effect of Empagliflozin on Major Renal Outcomes in the EMPEROR-Preserved Trial. Eur J Heart Fail. 2021;23(10):1798-9. doi: 10.1002/ejhf.2334.
14. Volpe M, Patrono C. The EMPEROR-Preserved Study: End of the Search for the "Phoenix" or Beginning of a New Season for Trials in Heart Failure with Preserved Ejection Fraction. Eur Heart J. 2021;42(45):4621-3. doi: 10.1093/eurheartj/ehab715.
15. Packer M, Zannad F, Anker SD. Heart Failure and a Preserved Ejection Fraction: A Side-by-Side Examination of the PARAGON-HF and EMPEROR-Preserved Trials. Circulation. 2021;144(15):1193-5. doi: 10.1161/CIRCULATIONAHA.121.056657.

SGLT2 Inhibitors and Sacubitril-Valsartan: How Trial Results will Revolutionize the Treatment of Heart Failure with Mildly Reduced Ejection Fraction

Miguel Morita Fernandes-Silva[1,2]
Universidade Federal do Paraná,[1] *Curitiba, PR – Brazil*
Quanta Diagnóstico por Imagem,[2] *Curitiba, PR – Brazil*

Left ventricular ejection fraction (EF) is a key parameter in the management of heart failure (HF) and a crucial biomarker for prognostic evaluation and therapeutic decision.[1] Patients with HF are classified into different categories according to EF. Although the concept of "normal" EF was introduced four decades ago, the cutoff values for normal and abnormal EF have considerably varied over time. In 2016, the European Society of Cardiology HF guidelines defined HF with reduced EF (HFrEF) as patients with EF below 40%, while HF with preserved EF (HFpEF) was the category for patients with EF equal to 50% or above.[2] To fill in the gap between the two categories, the term HF with mid-range EF was introduced. More recently, the guidelines considered more appropriate to rename this category to HF with mildly reduced EF (HFmrEF).[3,4] Why has the EF-based classification changed in recent years and how may this affect HF treatment?

In the 1980s, the first HF trials used in their design EF cutoffs to select patients with worse prognosis as an enrichment strategy, ie, they included patients based on a biomarker that improves design efficiency. Because patients with lower EF have worse prognosis and, therefore, higher rates of events, a relatively smaller sample size would be required to detect an effect. These trials used cutoff values for EF that ranged from < 45% to < 25% (Table) and were highly successful in finding effective therapies. In general, trials using a cutoff EF of < 40% consistently found drugs and devices for the treatment of HF that improved outcomes.

HF trials started including patients with EF above 40% in the early 2000s, covering the full EF range. Eligibility criteria for these trials varied from EF ≥ 40% to ≥ 50% (Table). Although the term "preserved EF" was used for these cutoff points, they differed from the cutoff values for normal EF established in the recommendations from echocardiographic reporting guidelines, which were based on the mean and 2 standard deviations for a healthy population: 52 to 72% for men and 54 to 74% for women.[5,6]

Current guidelines recommend treating all symptomatic patients with HFrEF with an angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor-neprylisin inhibitor (ARNi), a beta-blocker, a mineralocorticoid receptor antagonist (MRA), and a sodium-glucose cotransporter 2 inhibitor (SGLT2i) based on well-established evidence of their effect on reducing mortality. The success of these drugs in HFrEF was attempted to be reproduced in patients with HFpEF. ACEi, angiotensin receptor blocker (ARB), MRA, and ARNi have all been tested in HFpEF but have failed to show overall superiority for the primary endpoint (Table). This discrepancy suggests that HF is rather a heterogeneous disease with different mechanisms of progression depending on the phenotype.

Because no interventional trial was specifically dedicated to patients with HFmrEF, treatment of HFmrEF has been based on subanalysis of HFpEF trials, whose EF cutoff points included patients in this category. An analysis of the Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity (CHARM) program, combining the CHARM-added, CHARM- alternative and CHARM-preserved trials, showed that the benefit of candesartan on reducing the primary endpoint was observed in the EF range between 40 and 50%, but not above 50%.[7] A similar pattern was observed with spironolactone in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial,[8] with beta-blockers in patients in sinus rhythm in a meta-analysis,[9] and with sacubitril-valsartan.[10] In a subgroup analysis of the Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction (PARAGON-HF) trial, sacubitril-valsartan reduced the primary endpoint in the EF equal or below median (≤ 57%) but not above this cutoff point.[11] In a combined analysis of the PARADIGM-HF and PARAGON-HF trials across the continuum of EF, the treatment effect favoring sacubitril/valsartan appeared to extend to higher EF values (Figure).[10] In the past two years, regulatory agencies, including the United States Food and Drug Administration and the Brazilian National Health Surveillance Agency, have expanded the indication of sacubitril-valsartan for patients with HF, stating that the benefit is more clearly evident when EF is below normal.

Collectively, these data suggest that not only sacubitril-valsartan but also renin–angiotensin–aldosterone system and

Keywords

Heart Failure; Ejection Fraction; Angiotensin-converting Enzyme Inhibitor; Angiotensin receptor-neprylisin Inhibitor; Beta-blocker; Mineralocorticoid Receptor Antagonist; Sodium-glucose Cotransporter 2 Inhibitor.

Mailing Address: Miguel Morita Fernandes da Silva •
Departamento de Clínica Médica - Hospital de Clínicas da Universidade Federal do Paraná, 181 General Carneiro street, 10th floor. Postal Code 80060-900, Curitiba, PR - Brazil
E-mail: miguelmorita@ufpr.br
Manuscript received January 30, 2022, revised manuscript February 01, 2022, accpted February 16, 2022

DOI: https://doi.org/10.36660/abchf.20220013

Table 1 – Ejection fraction inclusion criteria for key phase III drug trials in heart failure

Treatment	HFrEF		HFpEF	
	Trial	EF cutoff (%)	Trial	EF cutoff (%)
ACEi	SOLVD[19]	≤ 35	PEP-CHF[20]	≥ 40
ARB	CHARM-Alternative[21]	≤ 40	CHARM-Preserved[22] I-PRESERVED[23]	> 40 ≥ 45
Beta-blocker	MERIT-HF[24] CIBIS-II[25] U.S. Carvedilol[26] COPERNICUS[27]	≤ 40 ≤ 35 ≤ 35 ≤ 25	J-DHF[28]	> 40
MRA	RALES[29] EMPHASIS-HF[30]	≤ 35 ≤ 35	TOPCAT[31] SPIRRIT-HFpEF[32] SPIRIT-HF[33] FINEARTS-HF[34]	≥ 45 ≥ 40 ≥ 40 ≥ 40
ARNi	PARADIGM-HF[35]	≤ 40	PARAGON-HF[11]	≥ 45
SGLT2i	DAPA-HF[37] EMPEROR-Reduced[38]	≤ 40 ≤ 40	DELIVER[39] EMPEROR-Preserved[40]	>40 >40

ACEi: angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor blocker; MRA: mineralocorticoid receptor antagonist; ARNi: angiotensin receptor-neprylisin inhibitor; CHARM: Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity; CIBIS-II: The Cardiac Insufficiency Bisoprolol Study II; COPERNICUS: Carvedilol Prospective Randomized Cumulative Survival Trial; DAPA-HF: Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; DELIVER: Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure; EMPEROR-Preserved: Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction; EMPEROR-Reduced: Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction; EMPHASIS-HF: Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; FINEARTS-HF: Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients With Heart Failure; I-PRESERVED: Irbesartan in Heart Failure with Preserved Ejection Fraction Study; MERIT-HF: Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; PARADIGM-HF: Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial; PARAGON-HF: Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction; PEP-CHF: Perindopril for Elderly People With Chronic Heart Failure Study; RALES: Randomized Aldactone Evaluation Study; SLGT2: sodium-glucose cotransporter 2 inhibitor; SOLVD: Studies of Left Ventricular Dysfunction; SPIRIT-HF: Spironolactone In The Treatment of Heart Failure; SPIRRIT-HFpEF: Spironolactone Initiation Registry Randomized Interventional Trial in Heart Failure With Preserved Ejection Fraction; TOPCAT: Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist.

sympathetic nervous system inhibitors have beneficial effects for HF in the "intermediate" EF range of 41 to 49%. These analyses provide insights that go beyond the treatment effect by indicating a role of these systems on disease progression in this category and helping understand part of the EF-related heterogeneity in HF. For instance, the contribution of noncardiac comorbidities on mortality is proportionally higher with increasing values of EF, particularly in the normal range.[12,13] This may explain why an intervention targeting the cardiovascular system is less likely to change the course of the disease in patients with normal EF. Patients with HFmrEF have intermediate features between HFrEF and HFpEF, but analyses from registries and clinical trials have shown that they display clinical characteristics that share more similarities with HFrEF than with HFpEF.[14] Accordingly, the recently published universal definition and classification of HF properly renamed the old "mid-range EF" category to "mildly reduced EF."[15]

Finally, the novel sodium-glucose cotransporter 2 (SGLT2) inhibitors have proven to be successful in HFrEF and paved the way for a new treatment target in HF. The question of whether this new drug class would also benefit patients with HFmrEF and HFpEF remained until the publication of the highly expected Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-preserved) trial in August 2021.[16] The EMPEROR-preserved trial included patients with HF and EF above 40% and showed that empagliflozin significantly reduced the primary outcome of cardiovascular death or HF hospitalization. Although this was mostly driven by a reduction in HF hospitalization, it was the first time that a HFpEF trial showed positive results for the primary outcome. A further analysis with data from the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction (EMPEROR-reduced) and EMPEROR-preserved trials was performed to evaluate whether the treatment effect differs across the EF categories. Similarly, the treatment effect of empagliflozin appeared to attenuate with higher EF values, but it remained consistent in patients with EF below 65%.[17] The results of the Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) trial, which tested the SGLT2 inhibitor dapagliflozin and is expected to be presented soon, will help understand whether there is a class effect. A trial of a slightly different class, the SGLT2-SGLT1 inhibitor sotagliflozin, included patients with diabetes and worsening HF and showed a significant reduction in the primary endpoint of cardiovascular death, hospitalization, and urgent visits for HF across all spectrum of EF.[18]

Despite its essential role in the management of HF, EF is an imperfect measure that is influenced by several biological phenomena. Its wide availability in clinical practice is counterbalanced by limitations to accurate measurement of EF. The intra- and interobserver variability of

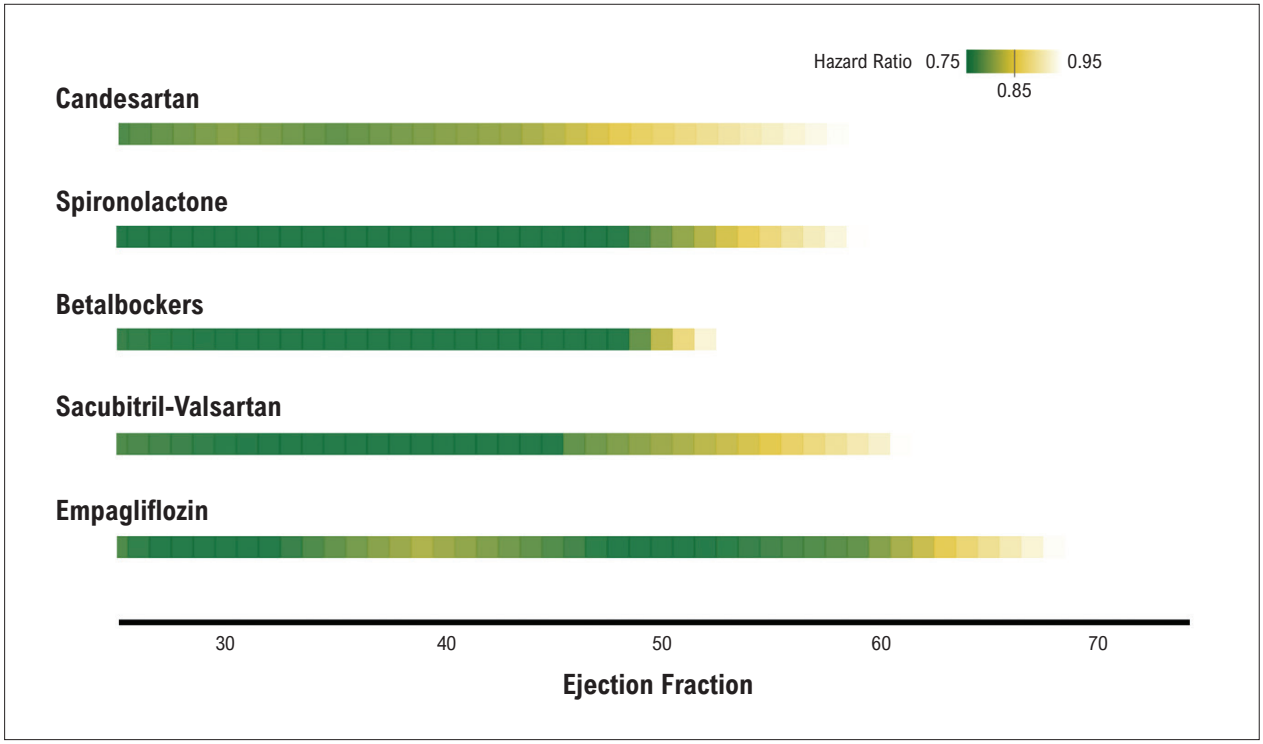


Figure 1 – *Treatment effect estimates of disease-modifying medications in heart failure across the spectrum of ejection fraction. Bar colors represent the reported estimated hazard ratios (HR) for each intervention according to ejection fraction. HR were extracted from respective published subanalysis from clinical trials:*
Candesartan: Lund et al.[7]
Spironolactone: Pitt et al.[29] and Solomon et al.[8]
Beta-blockers: Cleland et al.[9]
Sacubitril-valsartan: Solomon et al.[10]
Empagliflozin: Butler et al.[17]

EF measurements using echocardiogram has been reported as 8-21% and 6-13%, respectively, which limits the correct classification in categories with relatively narrow ranges of EF.[14] Some studies have evaluated the longitudinal changes of EF, showing considerable variation over time. In a Swedish registry, nearly 1/3 of patients switched to a lower EF category and 1/4 switched to a higher EF category over a median follow up duration of 1.4 years.[14] Because of the limitations of EF measurement, alternative methods have been suggested to better address the heterogeneity of HF, such as myocardial tissue characterization with magnetic resonance imaging, global longitudinal strain from speckle-tracking analysis with echocardiogram, multiple biomarker approaches, and proteomic characterization, but their use to guide the clinical management is still limited.[14]

Well-conducted trials are not only about finding effective therapies. They help understand the pathophysiology of a disease. HF classification has evolved together with the understanding of the disease. Despite the necessary strict and pragmatic criteria adopted in clinical trials, treatment effect of HF drugs has been consistently modified by EF as a continuous measure. Analysis from the latest HF trials of sacubitril-valsartan and SGLT2 inhibitor point to the same direction as those of renin–angiotensin–aldosterone system and sympathetic nervous system inhibitors, grouping together the categories of HF with EF below normal. I look forward to seeing what we will learn from the upcoming trials in HFpEF.

Author Contributions

Writing of the manuscript and Critical revision of the manuscript for intellectual content: Fernandes-Silva MM.

Potential Conflict of Interest

Received consulting and speaking fees from Novartis.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Savarese G, Stolfo D, Sinagra G, Lund LH. Heart Failure with Mid-range or Mildly Reduced Ejection Fraction. Nat Rev Cardiol. 2022;19(2):100-16. doi: 10.1038/s41569-021-00605-5.
2. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC) Developed with the Special Contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129-200. doi: 10.1093/eurheartj/ehw128.
3. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. Eur Heart J. 2021;42(36):3599-726. doi: 10.1093/eurheartj/ehab368.
4. Marcondes-Braga FG, Moura LAZ, Issa VS, Vieira JL, Rohde LE, Simões MV, et al. Emerging Topics Update of the Brazilian Heart Failure Guideline - 2021. Arq Bras Cardiol. 2021;116(6):1174-212. doi: 10.36660/abc.20210367.
5. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015;16(3):233-70. doi: 10.1093/ehjci/jev014.
6. Barberato SH, Romano MMD, Beck ALS, Rodrigues ACT, Almeida ALC, Assunção BMBL, et al. Position Statement on Indications of Echocardiography in Adults - 2019. Arq Bras Cardiol. 2019;113(1):135-81. doi: 10.5935/abc.20190129.
7. Lund LH, Claggett B, Liu J, Lam CS, Jhund PS, Rosano GM, et al. Heart Failure with Mid-range Ejection Fraction in CHARM: Characteristics, Outcomes and Effect of Candesartan Across the Entire Ejection Fraction Spectrum. Eur J Heart Fail. 2018;20(8):1230-9. doi: 10.1002/ejhf.1149.
8. Solomon SD, Claggett B, Lewis EF, Desai A, Anand I, Sweitzer NK, et al. Influence of Ejection Fraction on Outcomes and Efficacy of Spironolactone in Patients with Heart Failure with Preserved Ejection Fraction. Eur Heart J. 2016;37(5):455-62. doi: 10.1093/eurheartj/ehv464.
9. Cleland JGF, Bunting KV, Flather MD, Altman DG, Holmes J, Coats AJS, et al. Beta-Blockers for Heart Failure with Reduced, Mid-range, and Preserved Ejection Fraction: An Individual Patient-level Analysis of Double-blind Randomized Trials. Eur Heart J. 2018;39(1):26-35. doi: 10.1093/eurheartj/ehx564.
10. Solomon SD, Vaduganathan M, L Claggett B, Packer M, Zile M, Swedberg K, et al. Sacubitril/Valsartan Across the Spectrum of Ejection Fraction in Heart Failure. Circulation. 2020;141(5):352-61. doi: 10.1161/CIRCULATIONAHA.119.044586.
11. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, et al. Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. N Engl J Med. 2019;381(17):1609-20. doi: 10.1056/NEJMoa1908655.
12. Rohde LE, Claggett BL, Wolsk E, Packer M, Zile M, Swedberg K, et al. Cardiac and Noncardiac Disease Burden and Treatment Effect of Sacubitril/Valsartan: Insights from a Combined PARAGON-HF and PARADIGM-HF Analysis. Circ Heart Fail. 2021;14(3):e008052. doi: 10.1161/CIRCHEARTFAILURE.120.008052.
13. Wolsk E, Claggett B, Køber L, Pocock S, Yusuf S, Swedberg K, et al. Contribution of Cardiac and Extra-cardiac Disease Burden to Risk of Cardiovascular Outcomes Varies by Ejection Fraction in Heart Failure. Eur J Heart Fail. 2018;20(3):504-10. doi: 10.1002/ejhf.1073.
14. Savarese G, Stolfo D, Sinagra G, Lund LH. Heart Failure with Mid-range or Mildly Reduced Ejection Fraction. Nat Rev Cardiol. 2022;19(2):100-16. doi: 10.1038/s41569-021-00605-5.
15. Bozkurt B, Coats AJ, Tsutsui H, Abdelhamid M, Adamopoulos S, Albert N, et al. Universal Definition and Classification of Heart Failure: A Report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. J Card Fail. 2021:S1071-9164(21)00050-6. doi: 10.1016/j.cardfail.2021.01.022.
16. Anker SD, Butler J, Filippatos GS, Jamal W, Salsali A, Schnee J, et al. Evaluation of the Effects of Sodium-Glucose Co-Transporter 2 Inhibition with Empagliflozin on Morbidity and Mortality in Patients with Chronic Heart Failure and a Preserved Ejection Fraction: Rationale for and Design of the EMPEROR-Preserved Trial. Eur J Heart Fail. 2019;21(10):1279-87. doi: 10.1002/ejhf.1596.
17. Butler J, Packer M, Filippatos G, Ferreira JP, Zeller C, Schnee J, et al. Effect of Empagliflozin in Patients with Heart Failure Across the Spectrum of Left Ventricular Ejection Fraction. Eur Heart J. 2022;43(5):416-26. doi: 10.1093/eurheartj/ehab798.
18. Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, et al. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. N Engl J Med. 2021;384(2):117-28. doi: 10.1056/NEJMoa2030183.
19. Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of Enalapril on Survival in Patients with Reduced Left Ventricular Ejection Fractions and Congestive Heart Failure. N Engl J Med. 1991;325(5):293-302. doi: 10.1056/NEJM199108013250501.
20. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J. The Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) Study. Eur Heart J. 2006;27(19):2338-45. doi: 10.1093/eurheartj/ehl250.
21. Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, et al. Effects of Candesartan in Patients with Chronic Heart Failure and Reduced Left-Ventricular Systolic Function Intolerant to Angiotensin-Converting-Enzyme Inhibitors: The CHARM-Alternative Trial. Lancet. 2003;362(9386):772-6. doi: 10.1016/S0140-6736(03)14284-5.
22. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, et al. Effects of Candesartan in Patients with Chronic Heart Failure and Preserved Left-Ventricular Ejection Fraction: The CHARM-Preserved Trial. Lancet. 2003;362(9386):777-81. doi: 10.1016/S0140-6736(03)14285-7.
23. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, et al. Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction. N Engl J Med. 2008;359(23):2456-67. doi: 10.1056/NEJMoa0805450.
24. Hjalmarson A, Goldstein S, Fagerberg B, Wedel H, Waagstein F, Kjekshus J, et al. Effect of Metoprolol CR/XL in Chronic Heart Failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet. 1999;353(9169):2001-7.
25. Dargie HJ, Lechat P. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): A Randomised Trial. Lancet. 1999;353(9146):9-13.
26. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, et al. The Effect of Carvedilol on Morbidity and Mortality in Patients with Chronic Heart Failure. N Engl J Med. 1996;334(21):1349-55. doi: 10.1056/NEJM199605233342101.
27. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, et al. Effect of Carvedilol on Survival in Severe Chronic Heart Failure. N Engl J Med. 2001;344(22):1651-8. doi: 10.1056/NEJM200105313442201.
28. Yamamoto K, Origasa H, Hori M. Effects of Carvedilol on Heart Failure with Preserved Ejection Fraction: The Japanese Diastolic Heart Failure Study (J-DHF). Eur J Heart Fail. 2013;15(1):110-8. doi: 10.1093/eurjhf/hfs141.
29. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999;341(10):709-17. doi: 10.1056/NEJM199909023411001.
30. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, et al. Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms. N Engl J Med. 2011;364(1):11-21. doi: 10.1056/NEJMoa1009492.

31. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, et al. Spironolactone for Heart Failure with Preserved Ejection Fraction. N Engl J Med. 2014;370(15):1383-92. doi: 10.1056/NEJMoa1313731.

32. Spironolactone Initiation Registry Randomized Interventional Trial in Heart Failure with Preserved Ejection Fraction [Internet]. Bethesda: ClinicalTrials.gov. 2017 [cited 2022 Jan 28]. Available from: https://clinicaltrials.gov/ct2/show/NCT02901184?cond=spirrit+heart+failure&draw=2&rank=1.

33. Clinical Trials Register - Search for Spirit Heart Failure [Internet]. Amsterdam: EU Clinical Trials Register. c2022 [cited 2022 Jan 28]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=spirit+heart+failure.

34. Study to Evaluate the Efficacy (Effect on Disease) and Safety of Finerenone on Morbidity (Events Indicating Disease Worsening) & Mortality (Death Rate) in Participants with Heart Failure and Left Ventricular Ejection Fraction (Proportion of Blood Expelled Per Heart Stroke) Greater or Equal to 40% [Internet]. Bethesda: ClinicalTrials.gov. 2020 [cited 2022 Jan 28]. Available from: https://clinicaltrials.gov/ct2/show/NCT04435626?cond=NCT04435626&draw=2&rank=1.

35. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-Neprilysin Inhibition Versus Enalapril in Heart Failure. N Engl J Med. 2014;371(11):993-1004. doi: 10.1056/NEJMoa1409077.

36. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019;381(21):1995-2008. doi: 10.1056/NEJMoa1911303.

37. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. 2020;383(15):1413-24. doi: 10.1056/NEJMoa2022190.

38. Dapagliflozin Evaluation to Improve the LIVEs of Patients with Preserved Ejection Fraction Heart Failure [Internet]. Bethesda: ClinicalTrials.gov. 2021 [cited 2022 Jan 28]. Available from: https://clinicaltrials.gov/ct2/show/NCT03619213?cond=nct03619213&draw=2&rank=1.

39. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med. 2021;385(16):1451-61. doi: 10.1056/NEJMoa2107038.

Viewpoint

Clinical Profile-Based Pharmacological Sequencing for Heart Failure with Preserved Ejection Fraction

Evandro Tinoco Mesquita,[1,2,3,4] *Eduardo Thadeu de Oliveira Correia,*[1] *Letícia Mara dos Santos Barbetta*[1]

Universidade Federal Fluminense,[1] *Niterói, RJ – Brazil*

Instituto Cardiovascular do Complexo Hospitalar de Niterói,[2] *Niterói, RJ – Brazil*

Centro de Educação e Treinamento Edson Bueno – UnitedHealth Group,[3] *Rio de Janeiro, RJ – Brazil*

PROCEPI-DASA,[3] *Niterói, RJ – Brazil*

6ª enfermaria Santa Casa,[4] *Rio de Janeiro, RJ – Brazil*

Introduction

Heart failure (HF) is classically categorized into phenotypes according to left ventricular ejection fraction (EF), one of them being HF with preserved EF (HFpEF; EF ≥ 50%).[1] In the past decades, a myriad of drug therapies that reduce mortality and hospitalization rates for HF with reduced EF have emerged. However, although HFpEF accounts for about 50% of HF cases, to this date, only empagliflozin was shown to reduce HF hospitalization, and no drug reduced the risk for cardiovascular death in randomized clinical trials (RCTs).[2] One hypothesis that may explain the lack of therapies that reduce hard outcomes in HFpEF is the variety of phenotypes that constitute HFpEF as a syndrome.[3] Thus, in this paper, we discuss evidence from RCTs and post-hoc analyses of RCTs that may help improve HFpEF outcomes, aid clinicians, and pave the way for future RCTs.

Clinical phenotypes of heart failure with preserved ejection fraction

HFpEF is a clinical syndrome arising from the interaction of multiple comorbidities that leads to an inflammatory state that produces cardiac and extracardiac abnormalities.[3] Because of the diversity of comorbidities that can lead to HFpEF, this clinical syndrome is highly heterogenous, which may explain why RCTs investigating a one-size-fits-all treatment have failed to reduce cardiovascular mortality among patients with HFpEF.[3] Previous studies using machine-learning techniques have identified different phenogroups consisting of a combination of clinical features (pulmonary hypertension, lung congestion, atrial fibrillation, skeletal muscle weakness, and chronotropic incompetence),[4,5] as illustrated in Figure 1. In addition to different clinical characteristics, these phenogroups have prognostic particularities and appear to respond differently to medical therapies.[4,5] Therefore, classifying patients with HFpEF into phenogroups according to their clinical features could constitute a key aspect to guide medical therapy.

Keywords

Heart Failure; Mineralocorticoid Receptor Antagonists; Angiotensin-Converting Enzyme Inhibitors; Adrenergic Beta-Antagonists; Digoxin.

Mailing Address: Evandro Tinoco Mesquita •
Hospital Universitário Antônio Pedro - R. Marquês de Paraná, 303. Postal Code 24033-900, Centro, Niterói, RJ – Brazil
E-mail: etmesquita@gmail.com
Manuscript received February 25, 2022, revised manuscript February 25, 2022, accepted March 07, 2022

DOI: https://doi.org/10.36660/abchf.20220014

Evidence-based drug therapies for heart failure with preserved ejection fraction

As mentioned before, although there is a variety of drugs that improve outcomes for HF with reduced EF, this is not the case with HFpEF. One key step of HFpEF management is to treat etiologies and comorbidities (eg, hypertension, diabetes, coronary artery disease, obesity, anemia, chronic kidney disease, etc).[1] This may reduce not only disease progression but also HF hospitalization.[1] Regarding disease-modifying therapies, only empagliflozin is supported by robust evidence from an RCT to justify its use for HFpEF.[2] However, post-hoc analyses of RCTs indicate that other drug therapies may also reduce outcomes in HFpEF. This is mainly illustrated by the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial, in which spironolactone did not reduce the primary outcome in patients with HFpEF compared with placebo, although it was effective among patients with elevated natriuretic peptides.[6,7] Also, surprisingly, patients in the Americas experienced an 18% risk reduction in the primary outcome, whereas in Russia and Georgia, spironolactone did not improve prognosis.[6] A post-hoc analysis of the CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients (CHAMPION) trial also showed that changes in diuretic and vasodilator therapies according to pulmonary artery pressure reduced by 46% the incidence ratio of HF hospitalization in HFpEF with New York Heart Association (NYHA) class III.[8] Therefore, this may indicate that diuretics may not only control HF symptoms but also reduce HF hospitalization. Finally, although the Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction (PARAGON-HF) trial showed no benefit of sacubitril-valsartan for HFpEF, a prespecified analysis of this RCT showed that sacubitril-valsartan reduced the primary outcome in women with HFpEF due to a reduction in HF hospitalization.[9] In Table 1, we detail phase III RCTs that have investigated pharmacological therapies for HFpEF.

Clinical profile-based pharmacological sequencing for heart failure with preserved ejection fraction

As reviewed above, in addition to etiologic treatment, there are 3 drug therapies that may benefit patients with HFpEF based on RCTs (empagliflozin), post-hoc analyses of RCTs (mineralocorticoid receptor antagonists), and indirect

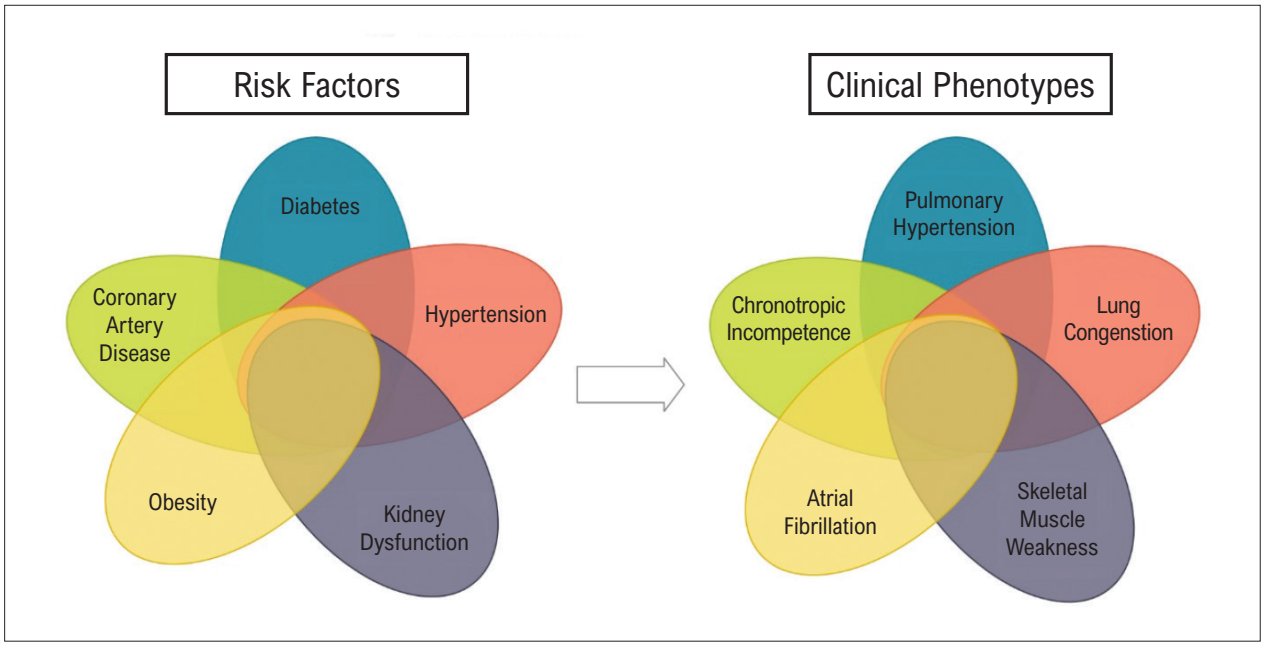


Figure 1 – *Interaction of cardiometabolic risk factors that produce a complex combination of clinical features with consequent unique phenotypes of heart failure with preserved ejection fraction.*

Table 1 – Phase III randomized controlled trials of pharmacological therapies for heart failure with preserved ejection fraction

Study	Drug	LVEF Range	Other Inclusion Criteria	All-Cause Mortality	CV Mortality	CV Death or HF Hospitalization	HF Hospitalization
PEP-CHF	Perindopril	LV wall motion index ≥ 1.4	Symptomatic HF treated with diuretics, diastolic dysfunction, age ≥ 70 years	1.09 (0.75-1.58)	0.98 (0.63-1.53)	NR	0.86 (0.61-1.20)
CHARM-Preserved	Candesartan	> 40%	NYHA class II-IV, history of CV hospitalization	NR	0.99 (0.80-1.22)	0.89 (0.77-1.03)	0.85 (0.72-1.01)
I-PRESERVE	Irbesartan	≥ 45%	NYHA class III-IV or NYHA class II with HF hospitalization in the past 6 months, age ≥ 60 years	1.00 (0.88-1.14)	1.01 (0.86-1.18)	0.96 (0.84-1.09)	0.95 (0.81-1.10)
PARAGON-HF	Sacubitril-valsartan	≥ 45%	NYHA class II-IV, left atrial enlargement or LV hypertrophy and elevated BNP ≥ 300 pg/mL or NT-proBNP ≥ 900 pg/mL or HF hospitalization in the past 9 months	0.97 (0.84-1.13)	0.95 (0.79-1.16)	0.87 (0.75-1.01)	0.85 (0.72-1.00)
TOPCAT	Spironolactone	≥ 45%	≥ 1 HF sign and ≥ 1 HF symptom, HF hospitalization within the past 12 months, or BNP ≥ 100 pg/mL or NT-proBNP ≥ 360 pg/mL, age ≥ 50 years	0.91 (0.77-1.08)	0.90 (0.73-1.12)	0.89 (0.77-1.04)	0.83 (0.69-0.99)
EMPEROR-Preserved	Empagliflozin	≥ 40%	NYHA class II-IV, 18 years or older, NT-proBNP > 300 pg/mL or NT-proBNP > 900 pg/mL for patients with HF and AF	1.00 (0.87-1.15)	0.91 (0.76-1.09)	0.79 (0.69-0.90)	0.73 (0.61-0.88)
DIG-PEF	Digoxin	> 45%	SR	0.99 (0.76-1.28)	1.00 (0.73-1.36)	0.88 (0.70-1.11)	0.79 (0.59-1.04)

AF: atrial fibrillation; CV: cardiovascular; HF: heart failure; LV: left ventricular; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal prohormone B-type natriuretic peptide; NYHA: New York Heart Association; S: sinus rhythm

evidence from RCTs (diuretics).[2,7,8] Also, personalizing HFpEF treatment according to clinical presentation and presence of risk factors, similar to what is done in other syndromes, could benefit patients with HFpEF and seems to be a better option than focusing on a one-size-fits-all treatment.[3] In Table 2, we suggest a pharmacological approach to treat patients with HFpEF according to their clinical presentation and risk factors, similar to that described by Shah et al.[3] but in light of new evidence from RCTs and post-hoc analyses reviewed in this paper.

Perspectives

The heterogeneity of HFpEF as a syndrome may explain why all RCTs have failed to observe a significant reduction in cardiovascular mortality in this population. New RCTs selecting a specific population of patients with HFpEF with a unique set of clinical features and risk factors might reveal effective medical therapies to be adopted by HF guidelines. For instance, Park et al. demonstrated that, for patients with HF with EF > 40% and a global longitudinal strain < 14%, the use of beta-blocker therapy was associated with improved survival, while for those with a global longitudinal strain > 14%, the same was not true.[10] However, the characterization of HFpEF phenotypes is under development, and there is still room for future large-scale multicenter studies using novel biomarkers and imaging techniques to better recognize HFpEF phenotypes.

Conclusions

Although HFpEF accounts for about 50% of HF cases, there is a lack of therapies that reduce cardiovascular death. Shifting from a one-size-fits-all approach to a clinical profile-based pharmacological strategy may be the key to produce a significant reduction in hard outcomes in HFpEF. However, although conceptually sound, this therapeutic model still needs to be validated by RCTs.

Author Contributions

Conception and design of the research, Analysis and interpretation of the data and Writing of the manuscript: Mesquita ET, Correia ETO, Barbetta LMS; Acquisition of data: Correia ETO; Critical revision of the manuscript for intellectual contente: Correia ETO, Barbetta LMS.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Table 2 – Pharmacological strategy for heart failure with preserved ejection fraction according to clinical profile and risk factors. Clinical phenotypes and table adapted from Shah et al.[3]

	Lung Congestion	Chronotropic Incompetence	Pulmonary Hypertension	Skeletal Muscle Weakness	Atrial Fibrillation
Obesity	Diuretics/MRA/SGLT2i/ ARNI (for women)/ caloric restriction	MRA/SGLT2i/ARNI (for women)/caloric restriction/atrial pacing	MRA/SGLT2i/ARNI (for women)/caloric restriction/PDE	MRA/SGLT2i/ARNI (for women)/caloric restriction/ exercise training	MRA/SGLT2i/ARNI (for women)/caloric restriction/ cardioversion or rate control/ anticoagulation
Diabetes	Diuretics/MRA/SGLT2i/ ARNI (for women)/ caloric restriction	MRA/SGLT2i/ARNI (for women)/caloric restriction/atrial pacing	MRA/SGLT2i/ARNI (for women)/caloric restriction/PDE	MRA/SGLT2i/ARNI (for women)/caloric restriction/ exercise training	MRA/SGLT2i/ARNI (for women)/caloric restriction/ cardioversion or rate control/ anticoagulation
Hypertension	Diuretics/MRA/SGLT2i/ ARNI (for women), ACEi or ARB	MRA/SGLT2i/ARNI (for women), ACEi or ARB/ atrial pacing	MRA/SGLT2i/ARNI (for women), ACEi or ARB/ PDE	MRA/SGLT2i/ARNI (for women), ACEi or ARB/ exercise training	MRA/SGLT2i/ARNI (for women), ACEi or ARB/ cardioversion or rate control/ anticoagulation
Kidney Dysfunction	Diuretics/MRA/SGLT2i/ ARNI (for women)/ ultrafiltration if needed	MRA/SGLT2i/ARNI (for women)/ultrafiltration if needed/atrial pacing if needed	MRA/SGLT2i/ARNI (for women)/ultrafiltration if needed/PDE	MRA/SGLT2i/ARNI (for women)/ultrafiltration if needed/exercise training	MRA/SGLT2i/ARNI (for women)/ultrafiltration if needed/cardioversion or rate control/anticoagulation
CAD	Diuretics/MRA/ SGLT2i/ARNI (for women), ACEi or ARB/ revascularization	MRA/SGLT2i/ARNI (for women), ACEi or ARB/ revascularization/atrial pacing if needed	MRA/SGLT2i/ARNI (for women), ACEi or ARB/ revascularization/PDE	MRA/SGLT2i/ARNI (for women), ACEi or ARB/ revascularization/exercise training	MRA/SGLT2i/ARNI (for women), ACEi or ARB/ revascularization/cardioversion or rate control/anticoagulation

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; ARNI: angiotensin receptor-neprilysin inhibitor; CAD: coronary artery disease; MRA: mineralocorticoid receptor antagonist; PDE: phosphodiesterase inhibitor; SGLT2i: sodium-glucose cotransporter 2 inhibitor.

References

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021 Sep 21;42(36):3599-3726. doi: 10.1093/eurheartj/ehab368.
2. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med. 2021;385(16):1451-61. doi: 10.1056/NEJMoa2107038.
3. Shah SJ, Kitzman DW, Borlaug BA, van Heerebeek L, Zile MR, Kass DA, et al. Phenotype-Specific Treatment of Heart Failure With Preserved Ejection Fraction: A Multiorgan Roadmap. Circulation. 2016;134(1):73-90. doi: 10.1161/CIRCULATIONAHA.116.021884.
4. Shah SJ, Katz DH, Selvaraj S, Burke MA, Yancy CW, Gheorghiade M, et al. Phenomapping for Novel Classification of Heart Failure with Preserved Ejection Fraction. Circulation. 2015;131(3):269-79. doi: 10.1161/CIRCULATIONAHA.114.010637.
5. Cohen JB, Schrauben SJ, Zhao L, Basso MD, Cvijic ME, Li Z, et al. Clinical Phenogroups in Heart Failure With Preserved Ejection Fraction: Detailed Phenotypes, Prognosis, and Response to Spironolactone. JACC Heart Fail. 2020;8(3):172-84. doi: 10.1016/j.jchf.2019.09.009.
6. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, et al. Spironolactone for Heart Failure with Preserved Ejection Fraction. N Engl J Med. 2014;370(15):1383-92. doi: 10.1056/NEJMoa1313731.
7. Girerd N, Ferreira JP, Rossignol P, Zannad F. A Tentative Interpretation of the TOPCAT Trial Based on Randomized Evidence from the Brain Natriuretic Peptide Stratum Analysis. Eur J Heart Fail. 2016;18(12):1411-14. doi: 10.1002/ejhf.621.
8. Adamson PB, Abraham WT, Bourge RC, Costanzo MR, Hasan A, Yadav C, et al. Wireless Pulmonary Artery Pressure Monitoring Guides Management to Reduce Decompensation in Heart Failure with Preserved Ejection Fraction. Circ Heart Fail. 2014;7(6):935-44. doi: 10.1161/CIRCHEARTFAILURE.113.001229.
9. McMurray JJV, Jackson AM, Lam CSP, Redfield MM, Anand IS, Ge J, et al. Effects of Sacubitril-Valsartan Versus Valsartan in Women Compared With Men With Heart Failure and Preserved Ejection Fraction: Insights From PARAGON-HF. Circulation. 2020;141(5):338-51. doi: 10.1161/CIRCULATIONAHA.119.044491.
10. Park JJ, Choi HM, Hwang IC, Park JB, Park JH, Cho GY. Myocardial Strain for Identification of β-Blocker Responders in Heart Failure with Preserved Ejection Fraction. J Am Soc Echocardiogr. 2019;32(11):1462-69.e8. doi: 10.1016/j.echo.2019.06.017.

Rethinking the Definition of Heart Failure Based on Ejection Fraction: Reflections with Impact on Therapy

Marcelo Iorio Garcia[1,2,3]

Universidade Federal do Rio de Janeiro,[1] *Rio de Janeiro, RJ – Brazil*
Hospital Pró-Cardíaco,[2] *Rio de Janeiro, RJ – Brazil*
Clínica São Vicente da Gávea,[3] *Rio de Janeiro, RJ – Brazil*

The universal definition of heart failure (HF) has been in a state of constant change in the last decades. It is necessary for the definition to be simple, comprehensible, and easily applied in clinically, as well as capable of differentiating patients' stages and severity, allowing stratification of levels of care, especially regarding candidates for specific therapies.

In relation to ejection fraction (EF), which is the subject of our reflection, the most recent document proposed the following subdivisions according to left ventricular ejection fraction (LVEF): HF with reduced ejection fraction (HFrEF), EF ≤ 40%; HF with midrange ejection fraction (HFmrEF), EF 41% to 49%; HF with preserved ejection fraction (HFpEF), EF ≥ 50%; and HF with improved EF (HFiEF), HF with EF ≤ 40% that has increased by at least 10 points, with the second measurement reaching > 40%.[1]

Let's discuss a few problems regarding EF. To put it simply, LVEF reflects the percentage of blood ejected by the left ventricle in relation to the amount of blood present in this cavity. Let's consider a few aspects. First, we will discuss contractile reserve (CR), which reflects the difference between resting contractility and contractility under stress, whether induced by exercise (stress test) or pharmacologically induced (for example, dobutamine).[2] How many of us use stress echocardiography (echo) to calculate CR, that is, left ventricular performance under stress? In short, we know nothing about CR, and we are satisfied with the information about resting EF. Second, let's analyze ventricular dimensions versus the concept of function. In Figure 1, we have 4 examples with different left ventricular dimensions, which nonetheless generate the same systolic volume (SV). A smaller left ventricle (for example, aortic stenosis or hypertrophic cardiomyopathy), under stress, will attempt to increase the SV in a hyperdynamic manner. At the other end of the spectrum, we have a large, hypodynamic left ventricle, which adapts to stress conditions through cavity dilation. Notice that SV is the same with different EF values. What do they have in common? The inability to generate greater SV under stress conditions.[3] EF is not telling us much.

Third, let's talk about Simpson's method, which has been recommended for calculating EF. We used the apical, 4- and 2-chamber (Ap4c and Ap2c) views of the left ventricle, assuming various geometric shapes to calculate ventricular volumes and EF. What do we omit to calculate using this strategy? In addition to these formulas working in symmetrically contracting ventricles, the use of these two sections does not include the inferolateral wall of the left ventricle, studied in the apical longitudinal section (also called the tricameral section). In other words, to encompass the left ventricle as a whole, we need the three-dimensional method (3D echo).[4] How many of us receive EF calculated by 3D in our reports? What is the availability of 3D echo in clinical practice? How many studies of HF with ischemic etiology have been presented over the years, considering only the traditional Simpson method? And how many of these had left ventricular lateral wall infarction? Figure 2 exemplifies these problems.

Finally, let's remember that changes in left ventricular preload and afterload influence the calculation of EF.[5] The presence of mitral regurgitation is very common in the clinical setting of HF. What is the "ideal" EF in the presence of severe mitral regurgitation (Figure 3)?

In spite of all these limitations, EF estimated by echo remains the method of choice. This tool is practical, easily applicable, and widely disseminated in the literature. Resonance plays an important role in cases with technical difficulties to echo and/or in doubtful cases, but there are important limitations to using it on a large scale.[6]

Also, what is the reason for subdividing according to EF, in particular the concept of mid-range (HFmrEF)? Let's analyze the definitions of HF from the past five decades:[7-11]

- 1980 – 1990: Inability to pump the blood necessary for metabolic demands or only pumping the blood at the expense of increased left ventricular filling pressures, basically a hemodynamic classification.
- 1991 – 2000: We practically considered only the HFrEF model (the dysfunction that we had in mind was basically systolic).
- 2001 – 2010: The concept of HFpEF is developed. Even with preserved systolic function, HF is diagnosed in the presence of signs and symptoms, structural changes (left atrial dilatation, left ventricular hypertrophy), and elevated natriuretic peptides.
- 2011 – 2020: In this decade, large studies on HFrEF were based on EF < 40%, even though the guidelines'

Keywords

Heart Failure; Stroke Volume; Therapeutics.

Mailing Address: Marcelo Iorio Garcia •
Av. Nossa Senhora de Copacabana, 647/814. Postal Code 22050-002, Copacabana, RJ - Brazil
E-mail: mioriogarcia@gmail.com
Manuscript received January 11, 2022, revised manuscript February 01, 2022, accepted February 16, 2022

DOI: https://doi.org/10.36660/abchf.20220016

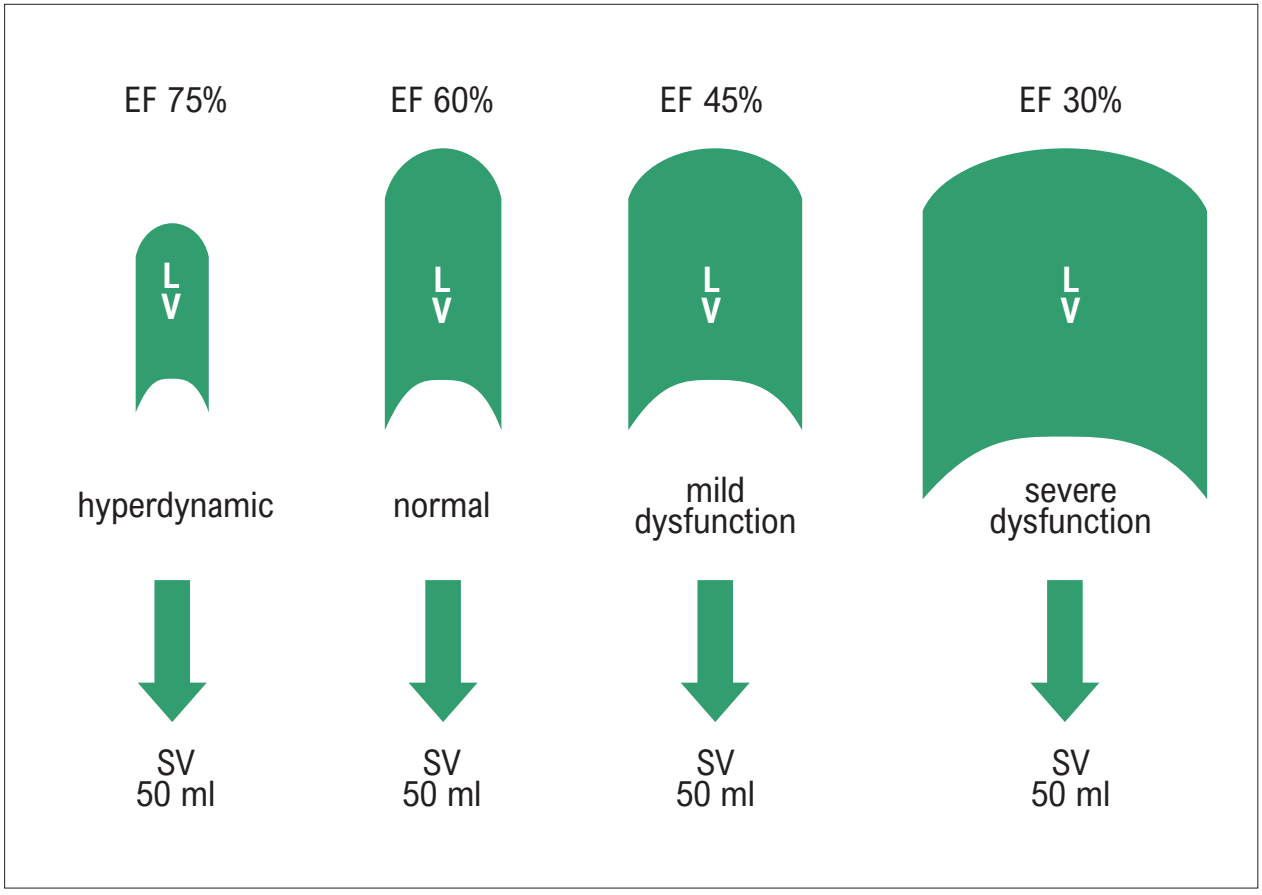
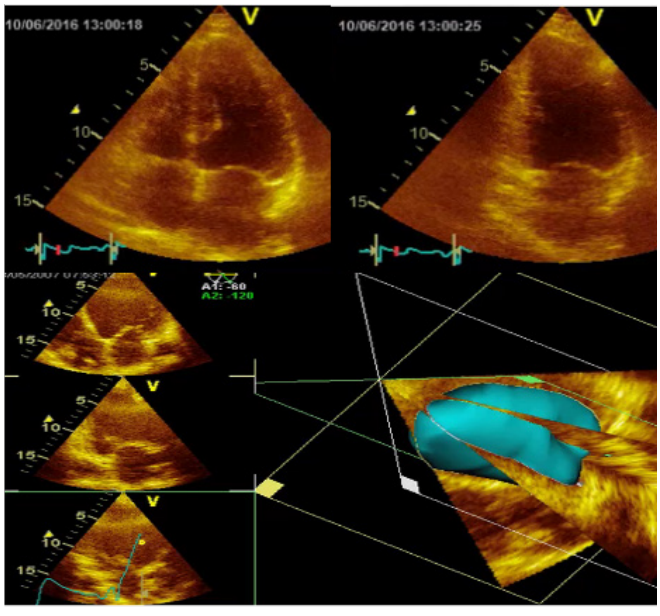


Figure 1 – *Schematic representation of different left ventricle (LV) sizes, with different ejection fraction (EF), which nonetheless generate the same systolic volume (SV)*



A – LVEF calculated by Simpson's method, using only Ap4c and Ap2c views.

B. LVEF calculated by the three-dimensional method, where cavity volumes are calculated in a global manner.

Figure 2 – *In image A, an example of calculation of left ventricular ejection fraction (LVEF) by Simpson's method. In image B, LVEF using the three-dimensional method.*

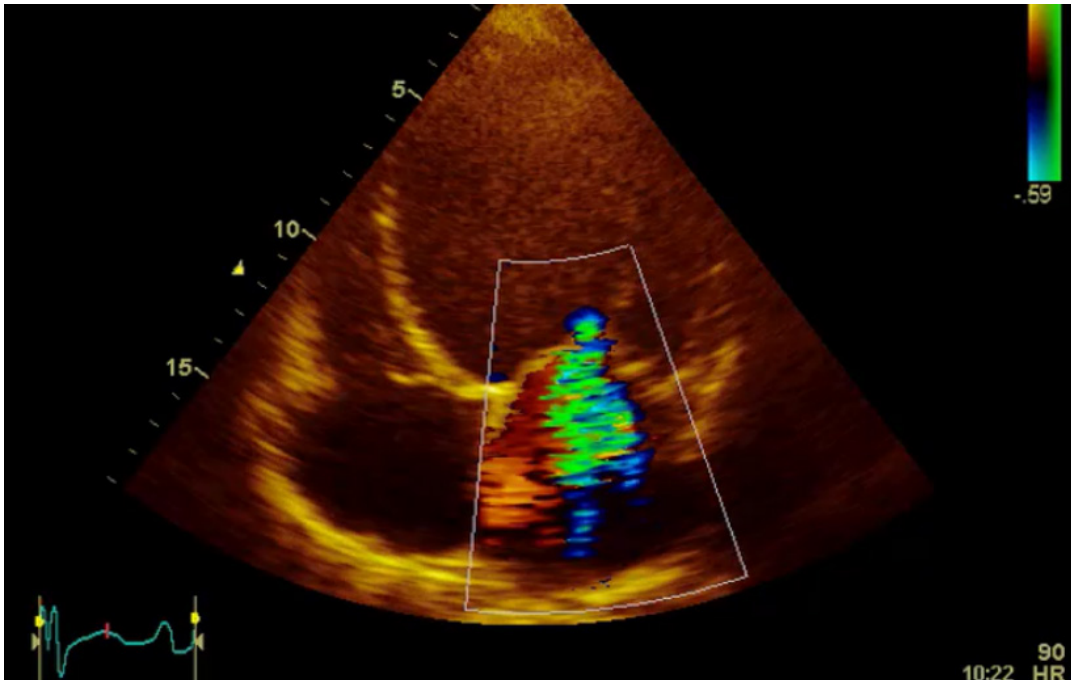


Figure 3 – *Mitral insufficiency secondary to valve ring dilation (tethering).*

definition had established EF < 50%. If we analyze the echo guidelines, the cutoff point is EF < 55%.

• 2021 – 2030: How will the next decade be? We have the following gap to study:

"Large studies of EF < 40% (HFrEF) versus EF > 50% to 55% (HFpEF)"

What happens in patients with intermediate ejection fraction? (EF 40% to 49%). The interest in this group, called HFmrEF, has gained strength, mainly after the results of the PARADIGM[12] study and, more recently, the PARAGON[13] study, both of which used sacubitril/valsartan instead of enalapril. Even in patients whose EF is still preserved, the closer to the lower limit of normality, the greater the benefits of the drug, especially in some specific scenarios, as demonstrated in women. Despite the favorable result in analysis of subgroups, in a syndrome as heterogeneous as HFpEF, when we are actually dealing with different diseases and different phenotypes, the strategy of studying intervention measures that can attenuate the evolution is always a challenge. If we cite only recent studies on HFrEF and HFpEF, we will see that the cut-off points in EF are quite heterogeneous, which makes it difficult to apply them in clinical practice.

The tool of EF will continue to be our main parameter; therefore, we must keep the following in mind: 1) EF is not a static parameter; it changes over time and with the evolution of the disease. 2) We need to consider other variables provided by echo, especially volume measurement. Hypervolemia is the main cause of decompensation in our patients. 3) How accurate is the method in differentiating EF 39% from EF 41%? This would place the patient in different categories, and the treatment decision will always be a clinical one. 4) How many of us actually receive estimated EF by Simpson's method (Figure 4)?

The evolution of imaging methods will certainly help us to standardize this important tool. Incorporating evaluation of left ventricular myocardial strain study in a friendlier manner and implementing predetermined machine learning algorithms[14] will play fundamental roles in the accurate determination and automated estimation of LVEF.

Author Contributions

Writing of the manuscript: Garcia MI

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

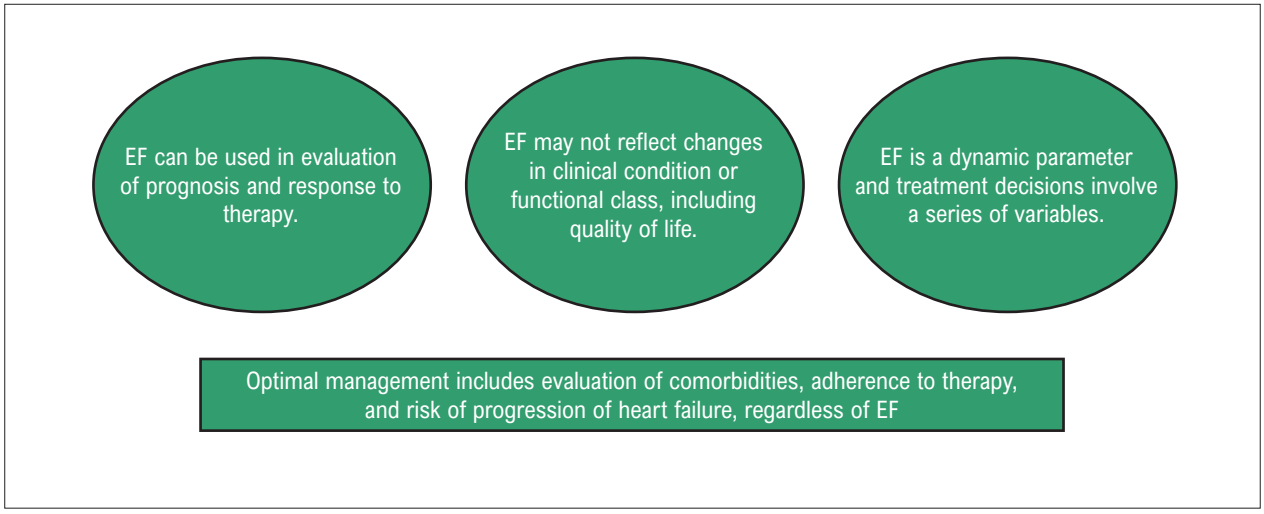


Figure 4 – *Ejection fraction (EF) in the context of heart failure.*

References

1. Bozkurt B, Coats AJS, Tsutsui H, Abdelhamid CM, Adamopoulos S, Albert N, et al. Universal Definition and Classification of Heart Failure: A Report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure: Endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. Eur J Heart Fail. 2021;23(3):352-80. doi: 10.1002/ejhf.2115.
2. Waddingham PH, Bhattacharyya S, Zalen JV, Lloyd G. Contractile Reserve as a Predictor of Prognosis in Patients with Non-ischaemic Systolic Heart Failure and Dilated Cardiomyopathy: A Systematic Review and Meta-analysis. Echo Res Pract. 2018;5(1):1-9. doi: 10.1530/ERP-17-0054.
3. Tarasoutchi F, Montera MW, Ramos AIO, Sampaio RO, Rosa VEE, Accorsi TAD, et al. Update of the Brazilian Guidelines for Valvular Heart Disease - 2020. Arq Bras Cardiol. 2020;115(4):720-75. doi: 10.36660/abc.20201047.
4. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28(1):1-39.e14. doi: 10.1016/j.echo.2014.10.003.
5. Dupuis M, Mahjoub H, Clavel MA, Côté N, Toubal O, Tastet L, et al. Forward Left Ventricular Ejection Fraction: A Simple Risk Marker in Patients With Primary Mitral Regurgitation. J Am Heart Assoc. 2017;6(11):e006309. doi: 10.1161/JAHA.117.006309.
6. Hendel RC, Patel MR, Kramer CM, Poon M, Hendel RC, Carr JC, et al. ACCF/ACR/SCCT/SCMR/ASNC/NASCI/SCAI/SIR 2006 Appropriateness Criteria for Cardiac Computed Tomography and Cardiac Magnetic Resonance Imaging: A Report of the American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group, American College of Radiology, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, American Society of Nuclear Cardiology, North American Society for Cardiac Imaging, Society for Cardiovascular Angiography and Interventions, and Society of Interventional Radiology. J Am Coll Cardiol. 2006;48(7):1475-97. doi: 10.1016/j.jacc.2006.07.003.
7. Wagner S, Cohn K. Heart Failure. A Proposed Definition and Classification. Arch Intern Med. 1977;137(5):675-8. doi: 10.1001/archinte.137.5.675.
8. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;128(16):240-327. doi: 10.1161/CIR.0b013e31829e8776.
9. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC). Developed with the Special Contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2016;18(8):891-975. doi: 10.1002/ejhf.592.
10. Tsutsui H, Isobe M, Ito H, Ito H, Okumura K, Ono M, et al. JCS 2017/JHFS 2017 Guideline on Diagnosis and Treatment of Acute and Chronic Heart Failure- Digest Version. Circ J. 2019;83(10):2084-184. doi: 10.1253/circj.CJ-19-0342.
11. Marcondes-Braga FG, Moura LAZ, Issa VS, Vieira JL, Rohde LE, Simões MV, et al. Emerging Topics Update of the Brazilian Heart Failure Guideline - 2021. Arq Bras Cardiol. 2021;116(6):1174-212. doi: 10.36660/abc.20210367.
12. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin Inhibition Versus Enalapril in Heart Failure. N Engl J Med. 2014;371(11):993-1004. doi: 10.1056/NEJMoa1409077.
13. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, et al. Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. N Engl J Med. 2019;381(17):1609-20. doi: 10.1056/NEJMoa1908655.
14. Seetharam K, Brito D, Farjo PD, Sengupta PP. The Role of Artificial Intelligence in Cardiovascular Imaging: State of the Art Review. Front Cardiovasc Med. 2020;7:618849. doi: 10.3389/fcvm.2020.618849.

Review Article

Treatment of Heart Failure Based on Natriuretic Peptide Levels: A Question That Has Yet to be Solved?

Carlos Eduardo Lucena Montenegro,[1,2,3] Taciana Queiroz Medeiros Gomes,[1] Ana Carla Alves de Souza Lyra,[1] Joyce Santana do Nascimento,[1] Luana do Amaral Dias[1]

Procape – Pronto Socorro Cardiológico de Pernambuco – Universidade de Pernambuco (UPE),[1] Recife, PE – Brazil

Cecom – Centro Cardiológico Ovídio Montenegro,[2] Recife, PE – Brazil

Real Hospital de Beneficência Portuguesa de Pernambuco,[3] Recife, PE – Brazil

Heart failure (HF) is one of the leading causes of death, hospitalization, and rehospitalization worldwide. In spite of advances in treatment with new medications, devices, and heart transplantation, the condition is still associated with significant morbidity and mortality.[1] One factor that likely contributes to this fact is the difficulty in titrating doses of drugs targeted at treating HF.[2]

Many professionals who deal with this disease have difficulties in recognizing early stages of deterioration and are reluctant to increase medications due to concerns regarding possible side effects, such as hypotension or renal failure.[3] There is also an endless search for a more objective parameter that can guide titration of medications.

In recent years, especially after the revolution set in motion by the neurohumoral theory of HF, biomarkers such as natriuretic peptides (B-type natriuretic peptide [BNP] and N-terminal pro-B-type natriuretic peptide [NT-proBNP]) have been used as more objective measures to diagnose and define prognosis of patients with HF.[3]

BNP is a neurohormone predominantly secreted by the cardiac ventricle in response to pressure[4] and/or volume overload.[5] The precursor of BNP is proBNP, a biologically inactive prohormone of 108 amino acids, stored in secretory granules in the myocytes. ProBNP is cleaved by protease into BNP, which is a physiologically active peptide of 32 amino acids, and NT-proBNP, which is a biologically inert peptide of 76 amino acids. Compared with BNP, NT-proBNP has a longer peptide sequence (76 versus 32 amino acids) and a longer half-life (60 to 120 minutes versus 15 to 20 minutes) (Figure 1).[6] BNP and NT-proBNP are biomarkers used for diagnosis, prognosis, risk stratification, and management of patients with HF.[7] BNP is not only a gold standard biomarker in HF; it also plays a key role in maintaining circulatory homeostasis, and, as its name indicates, it has natriuretic properties.[7]

Keywords

Heart Failure; Natriuretic Peptides; Natriuretic Peptide, Brain

Mailing Address: Carlos Eduardo Lucena Montenegro •
Rua Aviador Severiano Lins, 182. Ap. 2301. Postal Code 51020-060, Boa Viagem, Recife, PE – Brazil
E-mail: ce_montenegro@yahoo.com.br
Manuscript received Janeuary 25, 2022, revised manuscript February 01, 2022, accepted February 16, 2022

DOI: https://doi.org/10.36660/abchf.20220017

Multiple randomized clinical trials[3,9-15] have evaluated whether serial use of BNP could be useful to guide titration of medical therapy for HF, improving clinical outcomes in comparison to therapy guided only by symptoms. The trials were designed in a rather heterogeneous manner, and the results, especially those related to reduction of hospitalization and mortality, are controversial, depending on the BNP reduction strategy and the study population.

We emphasize that, in relation to use of BNP/NT-proBNP for diagnosis or prognostic definition of HF, there is no doubt as to their usefulness; in the most current guidelines and even in the recently published Universal Definition of Heart Failure, natriuretic peptides have been included as part of the diagnostic flowchart for HF, regardless of presentation phenotype (Figure 2).[16-18]

The following brief review attempts to summarize information about studies that have attempted to guide medical treatment of HF based on natriuretic peptide levels, as well as the clinical results presented to date.

Trials in chronic HF

Several studies have addressed the hypothesis that therapy guided by BNP or NT-proBNP would improve clinical outcomes in chronic HF.[1-12] Even though some of these studies demonstrated a reduction in clinical events, none of them, taken alone, was adequately powered to test the effect of this strategy on all-cause mortality.

One of the first published studies addressing this issue, published in 2000, was promising, suggesting a benefit in terms of mortality and hospitalization due to HF. Troughton et al.[19] demonstrated a reduction in total cardiovascular events (death, hospital admission, or decompensation of HF) (19 versus 54, p = 0.02), but their study had a small number of patients (69 patients) and a short-term follow-up.

Larger randomized trials were published later, including the 2009 TIME-CHF,[20] a multicenter study of patients over 60 years of age, with a number of patients about 7 times greater than the study by Troughton et al.[19] (499 patients). This trial showed no difference in BNP-guided versus symptom-guided therapy in relation to all-cause hospitalization-free survival (41% versus 40%, hazard ratio [HR] 0.91 [95% CI: 0.72 to 1.14]; p = 0.39) or quality of life of the patients included. There was only a reduction in all-cause hospitalization-free survival in the subgroup analysis of patients between 60 the ages of and 74 years and in hospitalization for HF (secondary outcome).

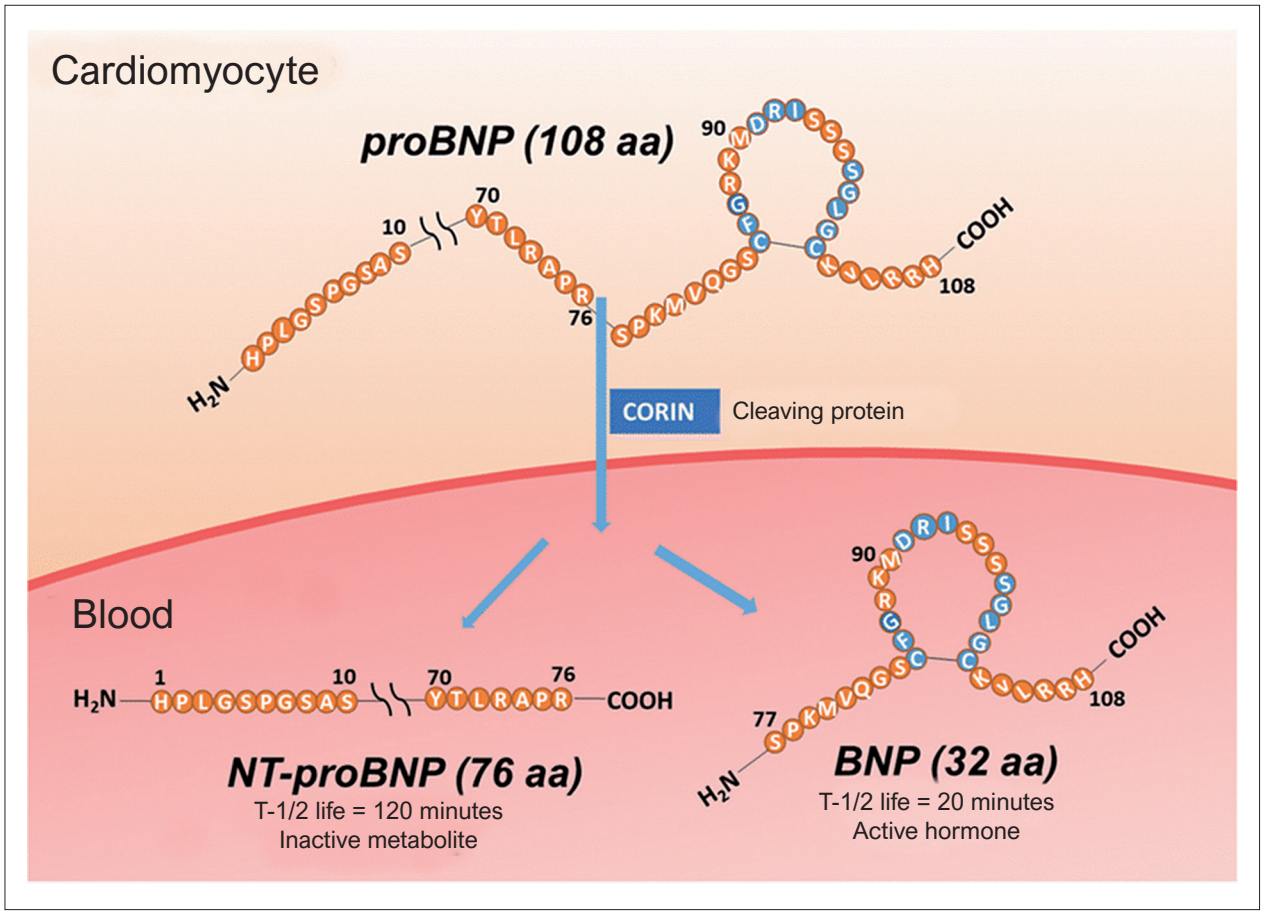


Figure 1 – *NT-proBNP and BNP synthesis pathways from proBNP. Adapted from Kim et al.[8]*

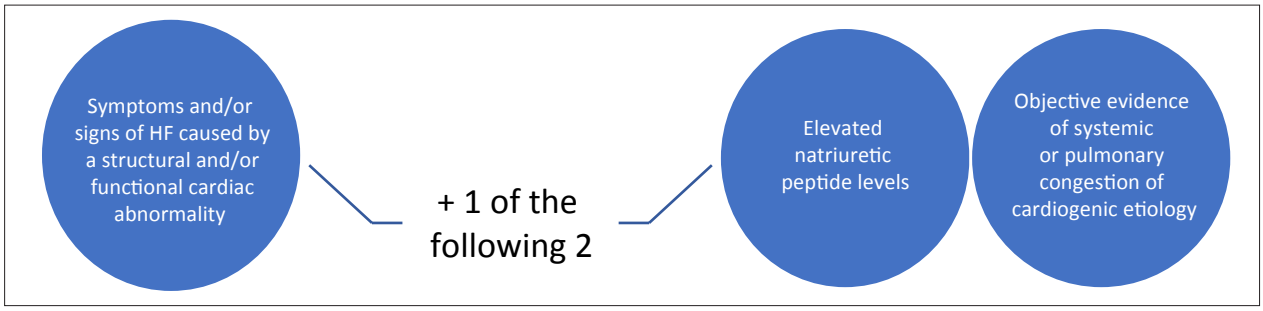


Figure 2 – *Universal definition of heart failure, 2021. Adapted from Bozkurt et al.[17]*

In 2013, Schou et al.[21] published another randomized clinical trial, with a total of 407 outpatients with HF, who were allocated to clinical management or clinical management and NT-proBNP monitoring, with 2.5 years of follow-up. In the event that NT-proBNP increased by more than 30%, a clinical checklist was performed, and treatment was modified. Patients had average age of 73 years and ejection fraction of 30%, and 85% of them were in NYHA functional class I or II. NT-proBNP monitoring did not improve the primary composite outcome (death or cardiovascular hospital admission) (HR 0.96, 95% CI: 0.71 to 1.29, p = 0.766), and it did not lead to a significant change in the pharmacological strategy.

A meta-analysis published in 2014 by Troughton et al.[15] compiled the majority of articles on the topic (11 randomized clinical trials), published between 2000 and 2012, and its primary outcome was analysis of all-cause mortality. In this meta-analysis, a reduction was observed in the primary outcome in the group whose treatment was guided by natriuretic peptide levels (HR 0.62 [0.45 – 0.86]; p = 0.004), but a survival benefit was only observed in younger patients (up to 75 years) (HR 0.62 [0.45 – 0.85]; p = 0.004)

and not in older patients (≥ 75 years) (0.98 [0.75 – 1.27]; p = 0.96). Secondary outcomes, such as hospitalization due to HF (0.80 [0.67 – 0.94]; p = 0.009) or cardiovascular disease (0.82 [0.67 – 0.99]; p = 0.048) were significantly lower in BNP-guided patients.

In contrast, the Cochrane database, in 2016, also published a systematic review with meta-analysis[7] on the topic, including 18 randomized controlled trials with 3660 participants (mean age range: 57 to 80 years). However, unlike the meta-analysis cited above, this one did not demonstrate any evidence for a decrease in all-cause mortality (HR 0.87, 95% CI: 0.76 to 1.01; patients = 3169; studies = 15), even when examining subgroups under or over 75 years of age, or for mortality due to HF (HR 0.84, 95% CI: 0.54 to 1.30; patients = 853; studies = 6) using natriuretic peptide-guided treatment. There was only a reduction in HF admission in the BNP-guided treatment group (38% versus 26%, HR 0.70, 95% CI: 0.61 to 0.80; patients = 1928; studies = 10), but there was no evidence for reduced all-cause hospital admission (57% versus 53%, HR 0.93, 95% CI: 0.84 to 1.03; patients = 1142; studies = 6).

In addition to those mentioned, at least 11 reviews were performed on the effects of treatment guided by natriuretic peptides: three narrative reviews (De Vecchis et al.,[22] DeBeradinis et al.,[23] Richards et al.[24]), one systematic review without meta-analysis (Balion et al.[25]) and 6 reviews that included meta-analyses (Felker et al.,[9] Porapakkham et al.,[10] Savarese et al.,[11] Li et al.,[12] De Vecchis et al.,[14] Li et al.,[26] Xin et al.[13]). Of these meta-analyses, 4 reported that peptide-guided therapy reduced all-cause mortality in patients with HF, and the other 2 reported no effects on all-cause mortality. All-cause hospital admission was analyzed in 2 of the reviews, and no effects were reported. Four reviews reported a decrease in HF admissions favoring natriuretic peptide-guided treatment. Moreover, 2 reviews examined adverse events and reported no significant difference between groups.

The meta-analysis by De Vecchis[14] cited above included 6 randomized controlled trials (n = 1775 patients), comparing BNP-guided therapy versus symptom-guided therapy in outpatients with chronic HF. This review reported that guided therapy decreased a composite outcome of mortality and HF hospitalizations during the follow-up period (odds ratio [OR] 0.64; 95% CI: 0.43 to 0.95; p = 0.028); however, when analyzing all-cause mortality alone, without including it in a composite outcome, there was no significant difference.

In the review with meta-analysis by Li et al.[12] also cited above, which included 11 randomized clinical trials (2414 patients), there was a lower risk of all-cause mortality (HR 0.83; 95% CI: 0.69 to 0.99; p = 0.035) and readmission due to HF (HR 0.75; 95% CI: 0.62 to 0.91; p = 0.004) in the BNP-guided therapy group. In subgroup analysis, readmissions due to HF were found to be lower, mainly in patients under 70 years of age (HR 0.45; 95% CI: 0.33 to 0.61; p = 0.000) or patients with higher baseline BNP (≥ 2114 pg/mL) (HR 0.53; 95% CI: 0.39 to 0.72). Moreover, in 2014, Li et al.[26] concluded sensitivity analyses and showed that the reduction in all-cause mortality and admission due to HF was observed especially in patients with reduced ejection fraction.

In 2017, the largest randomized and multicenter clinical trial to date was published, the GUIDE-IT,[27] which explored the same strategy as the previous ones but showed no difference between the groups in the primary outcome (time to first HF hospitalization or cardiovascular mortality) (32% versus 37%; HR 0.98; 95% CI: 0.79 to 1.22; p = 0.88), and the study was stopped early for futility, when 894 of 1100 patients were enrolled with a mean follow-up of 15 months. There was also no difference in the analysis of secondary outcomes (all-cause mortality, total HF hospitalizations, the individual components of the primary outcome, and adverse events) or NT-proBNP levels.

Finally, another meta-analysis, published by Pufulete et al.[3] in 2018, with 14 randomized clinical trials, studied the topic and found no significant difference in all-cause mortality (13 studies; HR 0.87, 95% CI: 0.75 to 1.01) or cardiovascular mortality (5 studies; OR 0.88, 95% CI: 0.67 to 1.16). For all-cause mortality, there was a significant interaction in the peptide-guided therapy group only when subgroups were evaluated. When analyzing the treatment strategy by age, there was a difference in the group under 75 years of age (p = 0.034, 11 studies, HR 0.70, 95% CI: 0.53 to 0.92 for patients < 75 years; and HR 1.07, 95% CI: 0.84 to 1.37, for patients ≥ 75 years), and when the groups were analyzed by ejection fraction, the group with HF with reduced ejection fraction had a significant result (p = 0.026, 11 studies, HR 0.84, 95% CI: 0.71 to 0.99 for patients with HF with reduced ejection fraction; and HR 1.33, 95% CI: 0.83 to 2.11 for patients with HF with preserved ejection fraction). When evaluating adverse events, there was evidence that they were significantly more frequent with BNP-guided therapy versus symptom-guided therapy, mainly at the expense of renal failure and hypotension (5 studies; OR 1.29; 95% CI: 1.04 to 1.60).

Trials in acute or acute decompensated heart failure

Seeing the importance of natriuretic peptides for diagnosis and prognosis in patients with acute HF, it was expected that other studies would attempt to establish treatment strategies guided by natriuretic peptides.[28-30] Carubelli et al. evaluated the strategy of using NT-proBNP (> 3000 ng/L before discharge) in 280 patients in order to intensify drug therapy for acute HF.[31] One of the groups had intensified drug therapy, mainly based on increased dose of diuretics (without a pre-specified NT-proBNP target), versus another group of patients who were discharged without any adjustments in therapy. The study was unable to demonstrate a difference in the results, and, when compared with only clinical evaluation, there was no evidence of improved prognosis.[31]

Within this same context, Stienen et al.[32] conducted a prospective randomized controlled study with the intention of evaluating the impact of hospital treatment following the pre-defined NT-proBNP reduction guideline (> 30% reduction from admission to discharge) versus conventional treatment.[31] The study population had NT-proBNP levels > 1700 ng/L. The primary composite outcome comprised all-cause mortality, HF readmissions within 180 days, and

death within 180 days of discharge. Secondary endpoints comprised all-cause mortality at 180 days, HF readmissions at 180 days, and a composite of all-cause mortality and HF readmissions at 90 days.

This study's Kaplan-Meier curve (Figure 3) demonstrates that all-cause mortality or HF readmission at 180 days after randomization occurred in 72 patients (36%) in the NT-proBNP-guided group and in 73 patients (36%) in the conventional therapy group (HR for NT-proBNP-guided therapy 0.96; 95% CI: 0.72 to 1.37; p = 0.99). In relation to secondary outcomes, there was also no statistical significance between the groups, in this context, demonstrating that guided therapy did not improve prognosis. It is worth highlighting that patients with NT-proBNP reduction of 30% had more cardiovascular events than patients in the control group, where treatment was not guided by the NT-proBNP value.[32]

In relation to adequate control of congestion in acute HF, several studies have demonstrated the relationship between residual congestion and increased morbidity and mortality.[33] O'Neill et al.[34] evaluated the correlation between hemodynamic measurements (through pulmonary artery catheter) and BNP levels in patients with severe acute HF, in measurements upon admission, with 12 and 36 hours of follow-up.[34] Serum BNP concentrations were not able to predict hemodynamic changes in these patients.

In contrast, retrospective analysis of the DOSE-AHF study, which involved hospitalized patients with diagnosis of acute HF, evaluated the relationship between 3 markers of decongestion in 72 hours: weight loss, fluid loss, and percentage reduction in serum NT-proBNP levels, in addition to symptomatic clinical improvement of dyspnea.[35] They also determined the relationship between each marker of decongestion and clinical outcomes at 60 days, such as death, first rehospitalization, and emergency department visit. The mean age of the patients was 66 years; mean ejection fraction was 35%, and 27% of the participants had ejection fraction ≥ 50%. Of the 3 measures of congestion improvement assessed, only reduced NT-proBNP was associated with dyspnea relief (r = 0.13; p = 0.04). However, reductions in the 3 measures were associated with improvement in time to death, first rehospitalization, and emergency department visit at 60 days (4 lbs of weight loss [HR 0.91; 95% CI: 0.85 to 0.97], 1000 mL of fluid loss [HR 0.94; 95% CI: 0.90 to 0.99], and 10% reduction in NT-proBNP [HR 0.95; 95% CI: 0.91 to 0.99]).[35]

Conclusions

Summarizing the data presented herein, the authors' impression is that this is a question that can be answered in several ways. The highly controversial data regarding HF therapy guided by natriuretic peptide levels in patients with chronic HF allow us to speculate that there is some applicability for their use in clinical practice, perhaps not routinely, but in a more specific niche of patients (bedridden patients, for example, where clinical assessment may be more impaired) and perhaps not taken alone, but in association with other markers of congestion, such as weight loss, urinary output, or even some that have been less tested, such as pulmonary ultrasound or bioimpedance. Trials in acute HF are already more uniform in not recommending this strategy for these patients. In conclusion, our impression is that the HF treatment strategy guided by BNP/NT-proBNP levels should not be used as a single strategy to guide HF treatment, based on the data that are currently available, but we cannot assert that this is a question that has already been solved, and new evidence may lead us to reevaluate our impression.

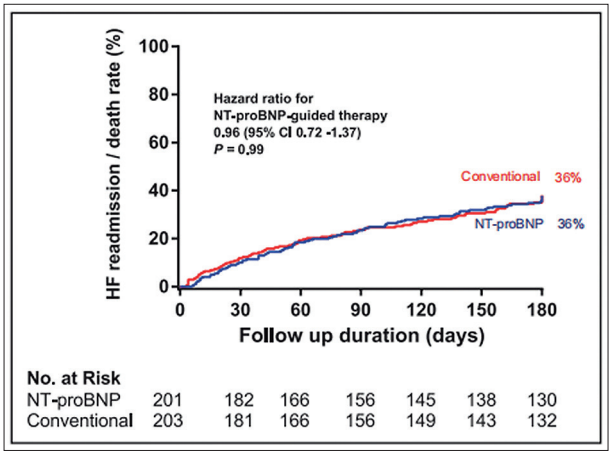


Figure 3 – *Kaplan-Meier cumulative survival curve for the study group.*

Author Contributions

Conception and design of the research: Montenegro CEL, Dias LA; Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual contente: Montenegro CEL, Gomes TQM, Lyra ACAS, Nascimento JS, Dias LA.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Hollingworth W, Biswas M, Maishman RL, Dayer MJ, McDonagh T, Purdy S, et al. The Healthcare Costs of Heart Failure During the Last Five Years of Life: A Retrospective Cohort Study. Int J Cardiol. 2016;224:132-8. doi: 10.1016/j.ijcard.2016.09.021.
2. Groote P, Isnard R, Clerson P, Jondeau G, Galinier M, Assyag P, et al. Improvement in the Management of Chronic Heart Failure since the Publication of the Updated Guidelines of the European Society of Cardiology. The Impact-Reco Programme. Eur J Heart Fail. 2009;11(1):85-91. doi: 10.1093/eurjhf/hfn005.
3. Pufulete M, Maishman R, Dabner L, Higgins JPT, Rogers CA, Dayer M, et al. B-type Natriuretic Peptide-guided Therapy for Heart Failure (HF): A Systematic Review and Meta-analysis of Individual Participant Data (IPD) and Aggregate Data. Syst Rev. 2018;7(1):112. doi: 10.1186/s13643-018-0776-8.
4. Nishikimi T, Maeda N, Matsuoka H. The Role of Natriuretic Peptides in Cardioprotection. Cardiovasc Res. 2006;69(2):318-28. doi: 10.1016/j.cardiores.2005.10.001.
5. Chen HH, Burnett JC. Natriuretic Peptides in the Pathophysiology of Congestive Heart Failure. Curr Cardiol Rep. 2000;2(3):198-205. doi: 10.1007/s11886-000-0069-3.
6. Yuting Z, Yanfeng M, Rongsheng K, Dongye L. Therapeutic Effects of BNP in Heart Failure, Good or Bad? Biomed Sci&Tech Res. 8(1):2018. doi: 10.26717/BJSTR.2018.08.001606.
7. McLellan J, Heneghan CJ, Perera R, Clements AM, Glasziou PP, Kearley KE, et al. B-type Natriuretic Peptide-guided Treatment for Heart Failure. Cochrane Database Syst Rev. 2016;12(12):CD008966. doi: 10.1002/14651858.CD008966.pub2.
8. Kim YS, Karisa N, Jeon WY, Lee H, Kim YC, Ahn J. High-Level Production of N-Terminal Pro-Brain Natriuretic Peptide, as a Calibrant of Heart Failure Diagnosis, in Escherichia Coli. Appl Microbiol Biotechnol. 2019;103(12):4779-88. doi: 10.1007/s00253-019-09826-8.
9. Felker GM, Hasselblad V, Hernandez AF, O'Connor CM. Biomarker-guided Therapy in Chronic Heart Failure: A Meta-analysis of Randomized Controlled Trials. Am Heart J. 2009;158(3):422-30. doi: 10.1016/j.ahj.2009.06.018.
10. Porapakkham P, Porapakkham P, Zimmet H, Billah B, Krum H. B-type Natriuretic Peptide-guided Heart Failure Therapy: A Meta-analysis. Arch Intern Med. 2010;170(6):507-14. doi: 10.1001/archinternmed.2010.35.
11. Savarese G, Trimarco B, Dellegrottaglie S, Prastaro M, Gambardella F, Rengo G, et al. Natriuretic Peptide-guided Therapy in Chronic Heart Failure: A Meta-Analysis of 2,686 Patients in 12 Randomized Trials. PLoS One. 2013;8(3):e58287. doi: 10.1371/journal.pone.0058287.
12. Li P, Luo Y, Chen YM. B-type Natriuretic Peptide-guided Chronic Heart Failure Therapy: A Meta-analysis of 11 Randomised Controlled Trials. Heart Lung Circ. 2013;22(10):852-60. doi: 10.1016/j.hlc.2013.03.077.
13. Xin W, Lin Z, Mi S. Does B-type Natriuretic Peptide-guided Therapy Improve Outcomes in Patients with Chronic Heart Failure? A Systematic Review and Meta-analysis of Randomized Controlled Trials. Heart Fail Rev. 2015;20(1):69-80. doi: 10.1007/s10741-014-9437-8.
14. De Vecchis R, Esposito C, Di Biase G, Ariano C, Giasi A, Cioppa C. B-type Natriuretic Peptide-guided Versus Symptom-guided Therapy in Outpatients with Chronic Heart Failure: A Systematic Review with Meta-analysis. J Cardiovasc Med (Hagerstown). 2014;15(2):122-34. doi: 10.2459/JCM.0b013e328364bde1.
15. Troughton RW, Frampton CM, Rocca HPB, Pfisterer M, Eurlings LW, Erntell H, et al. Effect of B-type Natriuretic Peptide-guided Treatment of Chronic Heart Failure on total Mortality and Hospitalization: An Individual Patient Meta-analysis. Eur Heart J. 2014;35(23):1559-67. doi: 10.1093/eurheartj/ehu090.
16. Marcondes-Braga FG, Moura LAZ, Issa VS, Vieira JL, Rohde LE, Simões MV, et al. Emerging Topics Update of the Brazilian Heart Failure Guideline - 2021. Arq Bras Cardiol. 2021;116(6):1174-212. doi: 10.36660/abc.20210367.
17. Bozkurt B, Coats A, Tsutsui H. Universal Definition and Classification of Heart Failure. J Card Fail. 2021:S1071-9164(21)00050-6. doi: 10.1016/j.cardfail.2021.01.022.
18. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. Eur Heart J. 2021;42(36):3599-726. doi: 10.1093/eurheartj/ehab368.
19. Troughton RW, Frampton CM, Yandle TG, Espiner EA, Nicholls MG, Richards AM. Treatment of Heart Failure Guided by Plasma Aminoterminal Brain Natriuretic Peptide (N-BNP) Concentrations. Lancet. 2000;355(9210):1126-30. doi: 10.1016/s0140-6736(00)02060-2.
20. Pfisterer M, Buser P, Rickli H, Gutmann M, Erne P, Rickenbacher P, et al. BNP-guided vs Symptom-guided Heart Failure Therapy: The Trial of Intensified vs Standard Medical Therapy in Elderly Patients with Congestive Heart Failure (TIME-CHF) Randomized Trial. JAMA. 2009;301(4):383-92. doi: 10.1001/jama.2009.2.
21. Schou M, Gustafsson F, Videbaek L, Andersen H, Toft J, Nyvad O, et al. Adding Serial N-terminal Pro Brain Natriuretic Peptide Measurements to Optimal Clinical Management in Outpatients with Systolic Heart Failure: A Multicentre Randomized Clinical Trial (NorthStar monitoring study). Eur J Heart Fail. 2013;15(7):818-27. doi: 10.1093/eurjhf/hft037.
22. De Vecchis R, Esposito C, Cantatrione S. Natriuretic Peptide-guided Therapy: Further Research Required for Still-unresolved Issues. Herz. 2013;38(6):618-28. doi: 10.1007/s00059-013-3772-8.
23. DeBeradinis B, Januzzi JL Jr. Use of Biomarkers to Guide Outpatient Therapy of Heart Failure. Curr Opin Cardiol. 2012;27(6):661-8. doi: 10.1097/HCO.0b013e3283587c4d.
24. Richards AM, Troughton RW. Use of Natriuretic Peptides to Guide and Monitor Heart Failure Therapy. Clin Chem. 2012;58(1):62-71. doi: 10.1373/clinchem.2011.165704.
25. Balion C, McKelvie R, Don-Wauchope AC, Santaguida PL, Oremus M, Keshavarz H, et al. B-type Natriuretic Peptide-guided Therapy: A Systematic Review. Heart Fail Rev. 2014;19(4):553-64. doi: 10.1007/s10741-014-9451-x.
26. Li Y , Pei H , Zhou X , et al . Efficacy, Modifiable Factors to Efficacy, Safety of B-type Natriuretic Peptide-Guided Heart Failure Therapy: A Meta-Analysis. Cardiology. 2014:66.
27. Felker GM, Anstrom KJ, Adams KF, Ezekowitz JA, Fiuzat M, Houston-Miller N, et al. Effect of Natriuretic Peptide-Guided Therapy on Hospitalization or Cardiovascular Mortality in High-Risk Patients with Heart Failure and Reduced Ejection Fraction: A Randomized Clinical Trial. JAMA. 2017;318(8):713-20. doi: 10.1001/jama.2017.10565.
28. Januzzi JL Jr, Chen-Tournoux AA, Christenson RH, Doros G, Hollander JE, Levy PD, et al. N-Terminal Pro-B-Type Natriuretic Peptide in the Emergency Department: The ICON-RELOADED Study. J Am Coll Cardiol. 2018;71(11):1191-200. doi: 10.1016/j.jacc.2018.01.021.
29. Bayés-Genís A, Lopez L, Zapico E, Cotes C, Santaló M, Ordonez-Llanos J, et al. NT-ProBNP Reduction Percentage During Admission for Acutely Decompensated Heart Failure Predicts Long-term Cardiovascular Mortality. J Card Fail. 2005;11(5 Suppl):S3-8. doi: 10.1016/j.cardfail.2005.04.006.
30. Patel AN, Southern WN. BNP-Response to Acute Heart Failure Treatment Identifies High-Risk Population. Heart Lung Circ. 2020;29(3):354-60. doi: 10.1016/j.hlc.2019.02.004.
31. Carubelli V, Lombardi C, Lazzarini V, Bonadei I, Castrini AI, Gorga E, et al. N-Terminal pro-B-type Natriuretic Peptide-guided Therapy in Patients Hospitalized for Acute Heart Failure. J Cardiovasc Med (Hagerstown). 2016;17(11):828-39. doi: 10.2459/JCM.0000000000000419.
32. Stienen S, Salah K, Moons AH, Bakx AL, van Pol P, Kortz RAM, et al. NT-proBNP (N-Terminal pro-B-Type Natriuretic Peptide)-Guided Therapy in Acute Decompensated Heart Failure: PRIMA II Randomized

Controlled Trial (Can NT-ProBNP-Guided Therapy During Hospital Admission for Acute Decompensated Heart Failure Reduce Mortality and Readmissions?). Circulation. 2018;137(16):1671-83. doi: 10.1161/CIRCULATIONAHA.117.029882.

33. Pourafkari L, Tajlil A, Nader ND. Biomarkers in Diagnosing and Treatment of Acute Heart Failure. Biomark Med. 2019;13(14):1235-49. doi: 10.2217/bmm-2019-0134.

34. O'Neill JO, Bott-Silverman CE, McRae AT 3rd, Troughton RW, Ng K, Starling RC, et al. B-type Natriuretic Peptide Levels are not a Surrogate Marker for Invasive Hemodynamics During Management of Patients with Severe Heart Failure. Am Heart J. 2005;149(2):363-9. doi: 10.1016/j.ahj.2004.05.051.

35. Kociol RD, McNulty SE, Hernandez AF, Lee KL, Redfield MM, Tracy RP, et al. Markers of Decongestion, Dyspnea Relief, and Clinical Outcomes Among Patients Hospitalized with Acute Heart Failure. Circ Heart Fail. 2013;6(2):240-5. doi: 10.1161/CIRCHEARTFAILURE.112.969246.

Review Article

Diuretics in Treatment of Heart Failure

Luis Fernando Bernal da Costa Seguro[1] *and José Leudo Xavier Júnior*[2]

Instituto do Coração do Hospital das Clínicas de São Paulo,[1] *São Paulo, SP – Brazil*

Hospital Israelita Albert Einstein,[2] *São Paulo, SP – Brazil*

Abstract

Heart failure is the leading cause of hospitalization in patients over 65 years of age, and, in most cases, patients present with signs and symptoms of congestion. Thus, diuretics play a prominent role and are among the most used drugs in heart failure. Although they have been used for decades, the lack of large controlled studies in the literature to support their use more adequately and the eventual development of resistance/tolerance are among the factors that make management of diuretics challenging.

Introduction

Heart failure (HF) affects 1% to 2% of the world population, afflicting more than 23 million people, and its prevalence increases with age. For example, in individuals over 85 years of age, prevalence can reach more than 17%. It is a serious public health problem, given its increasing financial impact. HF is the main cause of hospitalization among patients over 65 years of age, and, in the vast majority of cases, patients present with signs and symptoms resulting from pulmonary and systemic congestion. In this context, diuretics are extremely useful, as they are one of the primary factors in management of congestive syndrome.[1] During the past 3 decades, several drugs have emerged as protagonists in the treatment of HF, generating a real impact in terms of survival, as demonstrated by several multicenter, double-blind, controlled studies. Conversely, there is a lack of data in the literature, based on large controlled studies, to better support the use of diuretics, despite the fact that they have been used for more than half a century in patients with HF.[2]

Furthermore, another challenge is the eventual development of resistance to diuretics. In the context of patients with long-term HF, this occurrence is not uncommon, even though the actual incidence numbers are unknown, with several possible causal factors. These factors can occur alone or together. They range from inadequate dose to dietary issues, nutritional status, electrolyte disturbances, intestinal edema, and even renal dysfunction.[3] Diuretic resistance is an independent factor for mortality, due to both pump failure and sudden death.[4]

Accordingly, understanding how diuretics work, their interactions with the organism and with other diuretics, in addition to the mechanisms and factors that lead to diuretic resistance is of paramount importance so that we can obtain the maximum possible benefits from this longstanding class of drugs.

Keywords

Diuretics; Heart Failure; Heart Diseases.

Mailing Address: Leudo Xavier •
Rua Basílio da Cunha, 507, Apt 172, bloco 2. Postal Code 01544-001, Vila Deodoro, São Paulo, SP – Brazil
E-mail: leudoxavier@gmail.com
Manuscript received January 30, 2022, revised manuscript February 01, 2022, accepted February 22, 2022

DOI: https://doi.org/10.36660/abchf.20220018

Types of diuretics and their use in heart failure

Nephrons are the basic working structure of the kidneys. There are about one million nephrons in each kidney. Each day, about 180 liters of blood passes through the kidneys, where solutes and water are filtered by the glomeruli and reabsorbed or, eventually, eliminated, through the sequence of tubules that make up the structure of the nephron. One of the main solutes in the body is sodium (Na^+). Normally, about 99% of the Na^+ that has been filtered in the glomeruli is reabsorbed in the tubules, at different points and in different proportions, which, therefore, attracts water back to the organism.[5]

For the most part, diuretics are drugs that act to increase solute excretion by the nephrons, mainly of Na^+ salts, such as NaCl, in a process known as natriuresis. In response to the osmotic force of these solutes, there is a reduction in the reabsorption of water in the tubules, resulting in increased water excretion, which we call diuresis. Vasopressin inhibitors are an exception to this rule, as they block free water reabsorption channels in the collecting tubule.[6] The following are the most well known classes of diuretics: carbonic anhydrase inhibitors, osmotic diuretics, loop diuretics, thiazide diuretics, aldosterone receptor antagonists (also known as potassium-sparing diuretics), and vasopressin antagonists. There are also sodium-glucose cotransporter-2 (SGLT-2) inhibitors, which were originally developed for treatment of diabetes, but also have a diuretic effect. With the exception of spironolactone, which belongs to aldosterone antagonists, all diuretics need to be secreted into the tubular lumen in order to have an effect[7] (Figure 1).

Carbonic Anhydrase Inhibitors

Carbonic anhydrase is present in the basolateral and apical membranes of proximal convoluted tubular cells of nephrons, but also in the ciliary process of the eye, the choroid plexus, the intestine, and the pancreas. Its function is to catalyze the hydration of bicarbonate anions (HCO_3). In the proximal convoluted tubule, about two thirds of the Na^+ filtered by the glomeruli and practically all of the HCO_3^- are reabsorbed. Carbonic anhydrase inhibition reduces the availability of hydrogen ions (H^+), which prevents the exchange with luminal Na^+ by the Na^+/H^+ exchanger. Another effect is reduced HCO_3 reabsorption.[8] The prototype of carbonic anhydrase

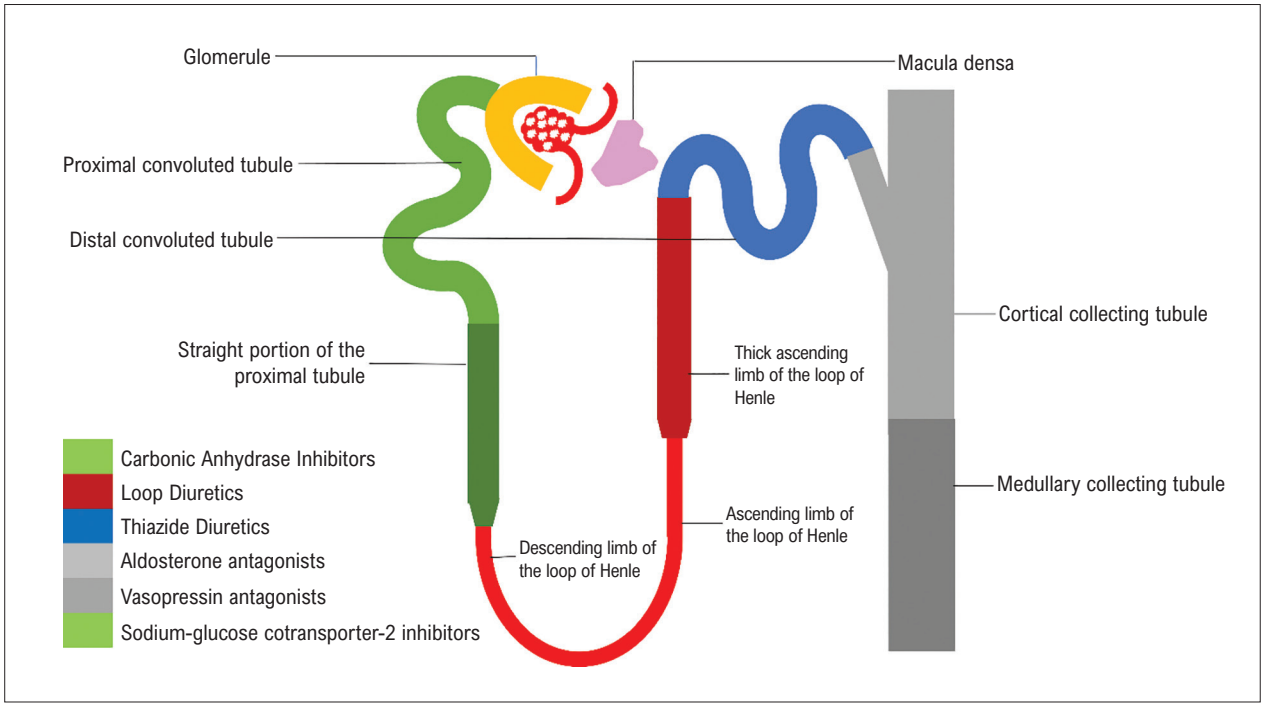


Figure 1 – *Representation of the nephron and its components (by the authors).*

inhibitors is acetazolamide. Currently, its main use is in treatment of glaucoma and metabolic alkalosis; however, before the 1950s, acetazolamide came to be widely used in treatment of HF, but its use was reduced with the advent of loop diuretics.[9] It is imaginable that, since acetazolamide acts in the site where the greatest reabsorption of Na^+ occurs, its diuretic effect would be more intense. However, a good part of this Na^+ that is not absorbed in the proximal tubule is reintegrated into the body in the thick limb of the loop of Henle (Figure 1). Therefore, combined use with loop diuretics would seem promising. However, a small study of 34 patients with acutely decompensated HF, DIURESIS-CHF demonstrated that acetazolamide and furosemide were better than furosemide alone in terms of nautriuresis, but there were no differences in mortality or hospital readmission. The study was interrupted before reaching the target N, which was 80, due to difficulties in randomizing patients.[10] A 2019 meta-analysis demonstrated that use of acetazolamide in patients with HF was able to reduce pH, increase natriuresis, and improve sleep apnea, which is a condition closely related to HF.[11] Two ongoing studies, Acetazolamide in Decompensated Heart Failure with Volume Overload (ADVOR)[12] and Acetazolamide in Patients with Acute Heart Failure (ACETA)[13] aim to evaluate the use of acetazolamide in combination with furosemide, in terms of efficiency in improving congestion in patients with HF and risk of diuretic resistance.

Loop Diuretics

This is undoubtedly the most used class of diuretics in HF, and it is part of the prescription for more than 90% of patients.[14] The most widely known representatives of this class are furosemide, torsemide, and bumetanide. Loop diuretics act in the thick portion of the ascending loop of Henle, on the Na-K-2Cl pump, where reabsorption of 25% of the filtered Na^+ occurs. Pump inhibition generates less reabsorption of Na^+ and Cl^-, resulting in increased diuresis.[6] They also act on another very similar cotransporter, Na-K-Cl, which is present in the ears, blood vessels, and macula densa. The inhibition of this other cotransporter in the vessels, associated with the well-known increase in prostaglandin synthesis by loop diuretics, generates venodilation, which may partially explain the reduction in pulmonary capillary pressure observed with the use of this class of diuretics.[15] However, the action on the macula densa implies an increase in renin and, consequently, in angiotensin II, which is a potent vasoconstrictor. There is no relationship between the type of diuretic, route of administration, or dosage applied and influence on inhibition of either type of cotransporter. The resulting action on the vessels is thus negligible. Eventual ototoxicity related to loop diuretics has been explained by the inhibition of Na-K-Cl in the ears.[16]

Loop diuretics are organic anions, which circulate bound to proteins. Therefore, instead of being filtered by the glomeruli, loop diuretics are secreted in the proximal tubule.[17] Non-steroidal anti-inflammatory drugs and uremic anions compete for the same structures that facilitate this secretion, which may contribute to resistance to this class of diuretics.[18] When administered orally, furosemide has a bioavailability that varies between 40% and 80%; it is highly influenced by food, which delays its absorption. Additionally, in patients with splanchnic edema, associated with reduced perfusion in this area, absorption, although it occurs fully, is slower, reducing the drug's plasma peak, which also contributes

to drug resistance. In patients with normal renal function, intravenous administration is about twice as potent.[19] In contrast, bumetanide and torsemide are not influenced by food; both have high bioavailability (> 90%), which makes oral and intravenous administration similar. It is known that bumetanide is 40 times more potent than furosemide; however, randomized studies comparing both are lacking.[20] The TORIC trial, which randomized 1377 patients to torsemide versus furosemide or other diuretics, showed greater symptom relief, in addition to good tolerability. Although it was not designed for this purpose, the study also demonstrated a tendency towards lower mortality with torsemide.[21] A meta-analysis of comparative studies of torsemide and furosemide also demonstrated a tendency toward reduced hospital readmissions and all-cause mortality.[22] Nonetheless, studies specifically designed to analyze mortality would be convenient to better evaluate torsemide.[23] The objective of the TRANSFORM-HF trial is to randomize 6000 hospitalized patients with HF and to compare torsemide with furosemide in terms of all-cause mortality.[24]

In HF, in order to achieve improvement in congestion, it is necessary to produce a negative water balance. It is known that, to generate this negative water balance with diuretics, the amount of Na^+ that leaves must be greater than the amount that enters. Increasing the dose of the diuretic and restricting dietary salt help to generate this fluid deficit. It is also known that, after the effect of the diuretic dose wears off, a phase of greater Na^+ retention by the nephrons follows, known as post-diuretic sodium retention.[25] Therefore, reducing the time interval between dosages also contributes to a negative balance. In other words, over the course of 24 hours, the longer the body is under the effect of the diuretic, the greater the likelihood of reaching euvolemia. This gave rise to the rationale behind the largest study on diuretics in the literature, the 2011 DOSE Trial. This randomized and multicenter trial aimed to compare intravenous use of furosemide in two scenarios: intermittent versus continuous infusion, and low versus high doses. The study randomized approximately 600 patients, and it showed significance in secondary outcomes (improved dyspnea and fluid loss) for high doses of diuretics (2.5 times the usual dose used at home) when compared to low doses.[26] There was a greater tendency toward worsened renal function; however, in a later evaluation, this greater elevation in creatinine had no clinical impact.[27] Regarding the comparison between continuous and intermittent use, there was no difference. Nevertheless, the study received some criticism related to the following: patients did not have criteria for diuretic resistance, when the continuous use of furosemide could possibly have some effect; continuous infusion at doses below what was recommended, and no loading dose was administered before initiating continuous infusion to reach the plasmatic equilibrium of drug concentrations.[28] Accordingly, the current guidelines recommend that, in cases of acutely decompensated HF, there should be an increase of at least 2.5 times the usual home dose of the diuretic, at least twice a day, and, in selected cases, such as diuretic resistance, cardiorenal syndrome, or severe right ventricular dysfunction, continuous infusion may be an alternative.[29]

Thiazide Diuretics

Thiazide diuretics work by blocking the sodium-chloride cotransporter in the distal convoluted tubule. Although they are less potent than loop diuretics, they may have a synergistic effect by leading to sequential nephron blockade.[30]

Thiazide diuretics bind to proteins, requiring adequate renal flow to be secreted into the tubules.[31] Thus, their effect may be reduced in the presence of severe renal dysfunction. By increasing the arrival of sodium from the collecting ducts, the exchange of sodium with potassium is increased, leading to potassium depletion, which is the most significant side effect.[30]

This class includes chlorthalidone, which is a drug with slower gastrointestinal absorption, with a longer time to start effect and a very long half-life (24 to 72 hours). Hydrochlorothiazide, on the other hand, has a shorter half-life (6 to 12 hours) and a shorter onset of action, and it should be administered close to the loop diuretic to potentiate its effect.[30,31] Although it is not a thiazide diuretic, metolazone acts in a similar manner. It is more potent than hydrochlorothiazide, and it maintains its action even when there is a severe reduction in the glomerular filtration rate.[30] When administered orally its effect is similar to that of an intravenous thiazide diuretic.[32]

Chronic use of loop diuretics leads to increased sodium avidity in the distal portion of the nephrons. This increased ability of the distal nephron to reabsorb sodium chloride eventually leads to a decline in natriuresis, which is known as the braking phenomenon.[33] This phenomenon is associated with nephron remodeling with hypertrophy of the distal convoluted tubule, collecting tubules, and collecting ducts, which has already been demonstrated in animal models.[34] One of the pathways that contribute to nephron remodeling is the activation of the renin-angiotensin-aldosterone system. Another mechanism is the fluid increase in the distal segments of the nephron, which leads to increased transepithelial flow and promotes synthesis of new proteins. There is also the effect of disturbances generated by diuretic use, such as metabolic alkalosis and hypokalemia, which strongly activate the sodium-chloride cotransporter.[33]

Table 1 – Loop diuretics[30]

	Duration	Initial dose	Maximum dose	Side effects
Furosemide	6 h	20 to 40 mg, once or twice daily	600 mg	Hyponatremia, hypokalemia, hypocalcemia, hypomagnesemia, ototoxicity
Bumetanide	4 to 6 h	0.5 to 1 mg, once or twice daily	10 mg	
Torsemide	12 to 16 h	10 to 20 mg, once daily	200 mg	

Accordingly, the association of a diuretic with action in the distal nephron can potentially help to reverse this phenomenon. Studies have demonstrated that the association of thiazide diuretics increases diuresis in patients who are already using loop diuretics, contributing to congestion control.[32,35,36] Therefore, even though there are not more robust prospective randomized studies demonstrating improvement in clinical outcomes with the use of thiazide diuretics for treatment of HF, their use, in association with loop diuretics, is recommended in the guidelines for treatment of HF.[37,38]

Aldosterone receptor antagonists

Aldosterone receptor antagonists act by modulating the expression and activation of sodium and potassium channels in the collecting ducts (distal nephron), reducing sodium and water absorption, and increasing potassium secretion.[31] Given that only 3% of the sodium filtered is reabsorbed in the collecting duct, the diuretic effect of this class is not very intense.[30] Nonetheless, they are often used to correct or prevent potassium deficiency generated by use of other classes of diuretics.

Spironolactone is a non-selective aldosterone receptor antagonist, and endocrine side effects (such as gynecomastia) are therefore common, whereas eplerenone, which is more selective for mineralocorticoid receptor, causes these side effects less.[39]

By reducing the deleterious effect of aldosterone on the cardiovascular system, the benefit of this class of diuretic in the treatment of chronic HF has been widely recognized.[4,41] However, its use in the treatment of decompensated HF has not been well established.

In a randomized study of 360 patients hospitalized with congestion, the use of a higher dose of spironolactone (100 mg per day) was not superior to placebo or a low dose of the drug (12.5 or 25 mg per day), which was maintained in the event that the patient was already using it. There was no improvement in the primary outcome (NT-proBNP variation) or secondary outcomes (clinical congestion score, dyspnea, urine output, or weight change). Likewise, there was no difference in safety outcomes (serum potassium and glomerular filtration rate), showing that the use of a higher dose of spironolactone in this context appears to be safe.[42]

In patients with heart failure with reduced ejection fraction (HFrEF) who are hospitalized for decompensation, early initiation of a low dose of aldosterone receptor antagonist (spironolactone 25 mg per day) or its maintenance in patients who are already using it may assist in reducing hypokalemia induced by diuretic treatment, in addition to increasing the chance that the patient will be discharged with optimal disease-modifying therapy, and it should be encouraged.[31]

Sodium-glucose cotransporter-2 inhibitors

SGLT-2 inhibitors inhibit sodium and glucose reabsorption in the proximal convoluted tubule, resulting in glucosuria, natriuresis, and increased urinary volume.[43]

Large multicenter studies that investigated the long-term effect of this class of medication in patients with HFrEF demonstrated a significant benefit in reducing morbidity and mortality.[44,45]

The DAPA-HF study, which compared the effect of dapagliflozin versus placebo, associated with optimal therapy, in 4744 patients with HFrEF, demonstrated a significant reduction in the primary endpoint of cardiovascular death or worsening of HF (26% reduction). When the outcomes were evaluated individually, a reduction was observed both in cardiovascular death (18% reduction) and in worsening of HF (30% reduction). Reduced death due to any cause, improved HF symptoms, and improved quality of life were also identified with use of the medication.[44]

Similarly, in the EMPEROR-Reduced study, which evaluated the use of empagliflozin compared to placebo in 3730 patients with HFrEF, a reduction was observed in the primary outcome of cardiovascular death or hospitalization due to HF (25% reduction) with the use of the drug. Moreover, the authors observed reduced decline in glomerular filtration rate in the group that used the drug, as well as a lower risk of serious kidney outcomes (chronic dialysis, kidney transplantation, more than 40% reduction in glomerular filtration rate).[45]

However, this benefit does not seem to be due exclusively to the increase in diuresis or to better glycemic control. The most accepted mechanisms are improved left ventricular wall tension secondary to decreased preload and afterload, improved cardiomyocyte metabolism and bioenergetics, myocardial sodium-hydrogen pump inhibition (which leads to higher concentration of calcium in the mitochondria), reduced cardiac necrosis and fibrosis, and alterations in the production of cytokines in the epicardial fat tissue.[46]

To date, the use of the drug to control congestion in patients with decompensated HF has not been well established.

In a sub-analysis of the DAPA-HF study, the diuretic dose used did not change significantly during follow-up in patients randomized to dapagliflozin when compared to the placebo group.[43]

Table 2 – Thiazide and thiazide-like diuretics[30]

	Duration	Initial dose	Maximum dose	Side effects
Hydrochlorothiazide	12 h	25 to 50 mg, once or twice daily	50 mg	Hyponatremia, hypokalemia, hypocalcemia, hypomagnesemia, hyperuricemia
Chlorthalidone	24 to 72 h	12.5 to 25 mg, once daily	100 mg	
Indapamide	36 h	2.5 mg, once daily	20 mg	
Metolazone	8 to 14 h	2.5 mg, once daily	20 mg	

On the other hand, the SOLOIST-WHF study, which evaluated the effect of sotagliflozin in patients with type 2 diabetes who had recently been hospitalized for worsening HF, showed a benefit for the drug when it was started close to decompensation. In this study, randomized patients started the medication before discharge (48.8%) or shortly after (median of 2 days after discharge). There was a reduction in the primary outcome of cardiovascular death and hospitalizations or urgent consultations for HF.[47]

Further studies are needed to define the role of this class of medication (which has some diuretic effect) in decompensated patients with pulmonary congestion and diuretic resistance.

Vasopressin antagonists

Although sodium retention is the greatest determinant of congestion in HF, hyponatremia, which indicates water accumulation, is common and confers worse prognosis.[29] Inappropriate elevation of vasopressin in HF plays a role in water retention, contributing to congestive symptoms and electrolyte disturbances.[48] Blockade of vasopressin receptors that are present in the collecting ducts inhibits the action of the antidiuretic hormone and increases the excretion of free water (aquaresis).[29]

In the EVEREST study, which evaluated the effect of tolvaptan (oral vasopressin-2 receptor antagonist) in patients with HFrEF who were hospitalized for decompensation, no improvement was observed in overall mortality, cardiovascular mortality, or hospitalization for HF, although improvement of dyspnea, greater weight loss, and reduced edema were identified during the first days, in addition to improved sodium levels in patients with hyponatremia.[48]

Subsequently, smaller studies evaluating early use of tolvaptan in acutely decompensated patients with diuretic resistance, renal dysfunction, or hyponatremia showed no improvement in dyspnea, notwithstanding greater weight loss.[49,50]

Although there is a rationale for using vasopressin antagonists in congested patients with hyponatremia, to date, in view of the results of the studies carried out, there is no recommendation for their use in the treatment of HF.

Approach to diuretic resistance

Diuretic resistance can be defined as the failure to reverse a congestive condition with an appropriate dose of diuretic and fluid and saline restriction. It is extremely common in patients with HF, but its real prevalence is unknown, largely due to the non-homogeneity of clinical studies (different diagnostic criteria, different populations, different doses of diuretics, etc).[3] However, it is known that diuretic resistance is an independent factor for mortality, due to both pump failure and sudden death.[4] Therefore, it must be promptly recognized. It has a multifactorial etiology, but inadequate diuretic doses are among the most frequent. It is known that, in HF, an adaptive phenomenon of "tolerance" to diuretics occurs over time, so that, in order to reach the same level of natriuresis as in healthy individuals, patients with HF require higher doses[3]. Table 3 lists some factors that may be involved in diuretic resistance. The search for possible causal factors is the first step in treating it.

Sequential nephron blockade

Up to 75% of cases of diuretic resistance in patients with acutely decompensated HF can be attributed to hyperactivation of Na-Cl transporters along the distal nephron, as a result of adaptive nephron remodeling.[51] Although this has not been properly tested in clinical studies, a plausible strategy in this scenario is sequential nephron blockade, with the introduction of a second, or even a third diuretic, which would prevent this adaptive hyperreabsorption of Na^+ in the distal convoluted tubules or collecting tubules, thus generating greater diuresis.[52]

Hypertonic saline solution

Another alternative for managing patients with diuretic resistance is the use of hypertonic saline solution (HSS) associated with high-dose intravenous furosemide. Studies evaluating this therapy in patients with acutely decompensated HF have shown improvement in short- and long-term outcomes. The rationale for using HSS is its osmotic effect, which would lead to mobilization of extravascular fluid, maintaining adequate intravascular content in spite of the increase in diuresis and natriuresis caused by the high diuretic dose.[53] Furthermore, it would act in correction of hyponatremia and hypochloremia, which may be correlated with diuretic resistance and mortality.[54]

In a study with 1771 patients with HFrEF who were hospitalized for decompensation, Paterna et al demonstrated that the group of patients who received HSS associated with a high dose of furosemide, compared to the group who received only the diuretic, showed increased urine output and serum sodium level, reduced hospitalization time, lower readmission rate, and lower mortality during follow-up.[55]

In a meta-analysis that included 11 randomized studies (total of 2987 patients), the authors observed that the use of HSS was associated with increased urine output, weight loss, increased urinary sodium excretion, correction of serum

Table 3 – Factors associated with diuretic resistance[29]

Inadequate diuretic dose	Neurohumoral activation
Poor adherence to water and saline restriction	Renal insufficiency
Visceral edema	Use of non-steroidal anti-inflammatory drugs
Poor splanchnic perfusion	Impaired drug secretion in the tubules
Poor renal perfusion	Malnutrition and hypoproteinemia
Nephron remodeling	

sodium, reduced serum creatinine, reduced length of hospital stay, and reduced rates of HF readmission and mortality. The benefits in the clinical outcomes identified, especially in mortality, seem to be disproportionate to the increase in urine output and weight loss. It is hypothesized that sodium loading could reduce adrenergic and renin-angiotensin system activation as well as their deleterious effects on the cardiovascular system.[53]

Given that the studies on this topic have some methodological problems, and the majority of them included a small number of patients, in addition to having used different HSS concentrations and forms of administration, more quality studies are needed to define the indications and the best way to use this intervention. Nevertheless, in patients hospitalized for decompensated HF with signs of hypervolemia and resistance to diuretic therapy, the use of HSS should be considered.[37]

Ultrafiltration

Ultrafiltration (UF) is similar to hemodialysis, but only fluid is removed from the body.[56] The first major study on this modality applied to HF was the UNLOAD Trial, in 2007. It showed greater weight loss and fewer hospitalizations with UF when compared to standard diuretic therapy, although there was no difference in serum creatinine or length of hospital stay.[57] It is worth underscoring that the study was strongly criticized due to the low dose of diuretics used and the lack of clarity regarding the calculation of the sample size. On the other hand, the CARRESS-HF study, in 2012, which compared UF with aggressive diuretic therapy in patients with HF and worsened renal function, showed no difference in relation to weight loss or improvement in symptoms, with significant worsening of creatinine in the UF group. Furthermore, UF was associated with a higher rate of adverse events.[58] This study was also strongly criticized for the following reasons: high crossover rate, UF conducted in patients who still had high urinary output, and exclusion of patients with more severe kidney disease (who might be the patients who would benefit most). Accordingly, the guidelines currently recommend the use of UF only as a rescue therapy, in cases where all of the previously mentioned measures have failed[59] (Figure 2).

Conclusion

In spite of the great advances in the last years, there are still many "blind spots" to knowledge regarding HF management, especially related to the use of diuretics, where there is still a lot of empiricism. Knowledge about the pharmacokinetic and pharmacodynamic properties of these drugs helps to improve the management of hypervolemia; nevertheless, larger and better clinical studies are needed.

Author Contributions

Writing of the manuscript and Critical revision of the manuscript for intellectual contente: Seguro LFBC e Xavier Júnior JL.

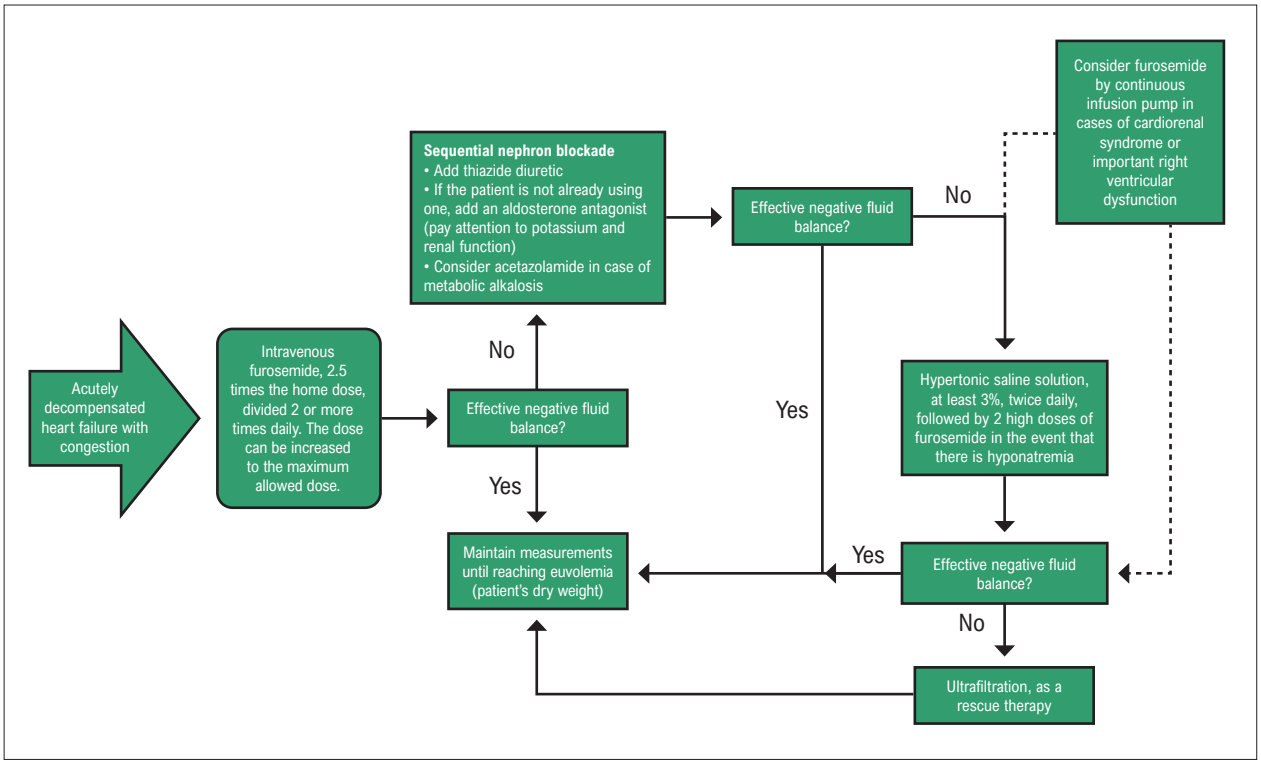


Figure 2 – *Flowchart for handling diuretic resistance in heart failure.*[29-31]

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Adams KF Jr, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, et al. Characteristics and Outcomes of Patients Hospitalized for Heart Failure in the United States: Rationale, Design, and Preliminary Observations from the First 100,000 Cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J. 2005;149(2):209-16. doi: 10.1016/j.ahj.2004.08.005.
2. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. 2009 Focused Update Incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation. J Am Coll Cardiol. 2009;53(15):1-90. doi: 10.1016/j.jacc.2008.11.013.
3. Ellison DH. Diuretic Therapy and Resistance in Congestive Heart Failure. Cardiology. 2001;96(3-4):132-43. doi: 10.1159/000047397.
4. Neuberg GW, Miller AB, O'Connor CM, Belkin RN, Carson PE, Cropp AB, et al. Prospective Randomized Amlodipine Survival Evaluation. Diuretic Resistance Predicts Mortality in Patients with Advanced Heart Failure. Am Heart J. 2002;144(1):31-8. doi: 10.1067/mhj.2002.123144.
5. Keller F, Hann A. Clinical Pharmacodynamics: Principles of Drug Response and Alterations in Kidney Disease. Clin J Am Soc Nephrol. 2018;13(9):1413-20. doi: 10.2215/CJN.10960917.
6. Brater DC. Diuretic Therapy. N Engl J Med. 1998;339(6):387-95. doi: 10.1056/NEJM199808063390607.
7. Lant A. Diuretics. Clinical Pharmacology and Therapeutic Use (Part I). Drugs. 1985;29(1):57-87. doi: 10.2165/00003495-198529010-00003.
8. Maren TH. Carbonic Anhydrase: Chemistry, Physiology, and Inhibition. Physiol Rev. 1967;47(4):595-781. doi: 10.1152/physrev.1967.47.4.595.
9. Massumi RA, Evans JM. Studies on the Continuous Use of a Carbonic Anhydrase Inhibitor (Diamox) in Ambulatory Patients. Am Heart J. 1955;49(4):626-32. doi: 10.1016/0002-8703(55)90081-8.
10. Verbrugge FH, Martens P, Ameloot K, Haemels V, Penders J, Dupont M, et al. Acetazolamide to Increase Natriuresis in Congestive Heart Failure at High Risk for Diuretic Resistance. Eur J Heart Fail. 2019;21(11):1415-22. doi: 10.1002/ejhf.1478.
11. Wongboonsin J, Thongprayoon C, Bathini T, Ungprasert P, Aeddula NR, Mao MA, et al. Acetazolamide Therapy in Patients with Heart Failure: A Meta-Analysis. J Clin Med. 2019;8(3):349. doi: 10.3390/jcm8030349.
12. Mullens W, Oost-Limburg Z. Acetazolamide in Decompensated Heart Failure with Volume OveRload (ADVOR). ClinicalTrials.gov Identifier: NCT03505788; 2018.
13. University of São Paulo General Hospital. Acetazolamide in Patients With Acute Heart Failure (ACETA). ClinicalTrials.gov Identifier: NCT03720288; 2018.
14. Felker GM. Diuretic Management in Heart Failure. Congest Heart Fail. 2010;16 (Suppl 1):68-72. doi: 10.1111/j.1751-7133.2010.00172.x.
15. Raftery EB. Haemodynamic Effects of Diuretics in Heart Failure. Br Heart J. 1994;72(2 Suppl):44-7. doi: 10.1136/hrt.72.2_suppl.s44.
16. Palmer LG, Schnermann J. Integrated Control of Na Transport Along the Nephron. Clin J Am Soc Nephrol. 2015;10(4):676-87. doi: 10.2215/CJN.12391213.
17. Delpire E, Lu J, England R, Dull C, Thorne T. Deafness and Imbalance Associated with Inactivation of the Secretory Na-K-2Cl Co-Transporter. Nat Genet. 1999;22(2):192-5. doi: 10.1038/9713.
18. Hasegawa M, Kusuhara H, Adachi M, Schuetz JD, Takeuchi K, Sugiyama Y. Multidrug Resistance-Associated Protein 4 is Involved in the Urinary Excretion of Hydrochlorothiazide and Furosemide. J Am Soc Nephrol. 2007;18(1):37-45. doi: 10.1681/ASN.2005090966.
19. Eraly SA, Vallon V, Vaughn DA, Gangoiti JA, Richter K, Nagle M, et al. Decreased Renal Organic Anion Secretion and Plasma Accumulation of Endogenous Organic Anions in OAT1 Knock-Out Mice. J Biol Chem. 2006;281(8):5072-83. doi: 10.1074/jbc.M508050200.
20. Roush GC, Kaur R, Ernst ME. Diuretics: A Review and Update. J Cardiovasc Pharmacol Ther. 2014;19(1):5-13. doi: 10.1177/1074248413497257.
21. Nappi JM. A Retrospective Evaluation of the Efficacy of Intravenous Bumetanide and Comparison of Potency with Furosemide. Pharm Pract (Granada). 2013;11(1):44-50. doi: 10.4321/s1886-36552013000100008.
22. Cosín J, Díez J. Torasemide in Chronic Heart Failure: Results of the TORIC Study. Eur J Heart Fail. 2002;4(4):507-13. doi: 10.1016/s1388-9842(02)00122-8.
23. DiNicolantonio JJ. Should Torsemide be the Loop Diuretic of Choice in Systolic Heart Failure? Future Cardiol. 2012;8(5):707-28. doi: 10.2217/fca.12.54.
24. Duke University. The Torsemide Comparison with Furosemide for Management of Heart Failure (TRANSFORM-HF) trial (NCT03296813); 2017.
25. Arcand J, Ivanov J, Sasson A, Floras V, Al-Hesayen A, Azevedo ER, et al. A High-Sodium Diet is Associated with Acute Decompensated Heart Failure in Ambulatory Heart Failure Patients: A Prospective Follow-up Study. Am J Clin Nutr. 2011;93(2):332-7. doi: 10.3945/ajcn.110.000174.
26. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, et al. Diuretic Strategies in Patients with Acute Decompensated Heart Failure. N Engl J Med. 2011;364(9):797-805. doi: 10.1056/NEJMoa1005419.
27. Brisco MA, Zile MR, Hanberg JS, Wilson FP, Parikh CR, Coca SG, et al. Relevance of Changes in Serum Creatinine During a Heart Failure Trial of Decongestive Strategies: Insights From the DOSE Trial. J Card Fail. 2016;22(10):753-60. doi: 10.1016/j.cardfail.2016.06.423.
28. Hanberg JS, Tang WHW, Wilson FP, Coca SG, Ahmad T, Brisco MA, et al. An Exploratory Analysis of the Competing Effects of Aggressive Decongestion and High-Dose Loop Diuretic Therapy in the DOSE Trial. Int J Cardiol. 2017;241:277-82. doi: 10.1016/j.ijcard.2017.03.114.
29. Ellison DH, Felker GM. Diuretic Treatment in Heart Failure. N Engl J Med. 2017;377(20):1964-75. doi: 10.1056/NEJMra1703100.
30. Casu G, Merella P. Diuretic Therapy in Heart Failure - Current Approaches. Eur Cardiol. 2015;10(1):42-7. doi: 10.15420/ecr.2015.10.01.42.
31. Mullens W, Damman K, Harjola VP, Mebazaa A, Brunner-La Rocca HP, Martens P, et al. The Use of Diuretics in Heart Failure with Congestion - A Position Statement from the Heart Failure Association of the European

Society of Cardiology. Eur J Heart Fail. 2019;21(2):137-55. doi: 10.1002/ejhf.1369.

32. Shulenberger CE, Jiang A, Devabhakthuni S, Ivaturi V, Liu T, Reed BN. Efficacy and Safety of Intravenous Chlorothiazide versus Oral Metolazone in Patients with Acute Decompensated Heart Failure and Loop Diuretic Resistance. Pharmacotherapy. 2016;36(8):852-60. doi: 10.1002/phar.1798.

33. Felker GM, Ellison DH, Mullens W, Cox ZL, Testani JM. Diuretic Therapy for Patients with Heart Failure: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020;75(10):1178-95. doi: 10.1016/j.jacc.2019.12.059.

34. Rao VS, Planavsky N, Hanberg JS, Ahmad T, Brisco-Bacik MA, Wilson FP, et al. Compensatory Distal Reabsorption Drives Diuretic Resistance in Human Heart Failure. J Am Soc Nephrol. 2017;28(11):3414-24. doi: 10.1681/ASN.2016111178.

35. Palazzuoli A, Ruocco G, Severino P, Gennari L, Pirrotta F, Stefanini A, et al. Effects of Metolazone Administration on Congestion, Diuretic Response and Renal Function in Patients with Advanced Heart Failure. J Clin Med. 2021;10(18):4207. doi: 10.3390/jcm10184207.

36. Cox ZL, Hung R, Lenihan DJ, Testani JM. Diuretic Strategies for Loop Diuretic Resistance in Acute Heart Failure: The 3T Trial. JACC Heart Fail. 2020;8(3):157-68. doi: 10.1016/j.jchf.2019.09.012.

37. Rohde LEP, Montera MW, Bocchi EA, Clausell NO, Albuquerque DC, Rassi S, et al. Diretriz Brasileira de Insuficiência Cardíaca Crônica e Aguda. Arq Bras Cardiol. 2018;111(3):436-539. doi: 10.5935/abc.20180190.

38. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. Eur Heart J. 2021;42(36):3599-726. doi: 10.1093/eurheartj/ehab368.

39. Struthers A, Krum H, Williams GH. A Comparison of the Aldosterone-Blocking Agents Eplerenone and Spironolactone. Clin Cardiol. 2008;31(4):153-8. doi: 10.1002/clc.20324.

40. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999;341(10):709-17. doi: 10.1056/NEJM199909023411001.

41. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, et al. Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms. N Engl J Med. 2011;364(1):11-21. doi: 10.1056/NEJMoa1009492.

42. Butler J, Anstrom KJ, Felker GM, Givertz MM, Kalogeropoulos AP, Konstam MA, et al. Efficacy and Safety of Spironolactone in Acute Heart Failure: The ATHENA-HF Randomized Clinical Trial. JAMA Cardiol. 2017 Sep 1;2(9):950-8. doi: 10.1001/jamacardio.2017.2198.

43. Jackson AM, Dewan P, Anand IS, Bělohlávek J, Bengtsson O, de Boer RA, et al. Dapagliflozin and Diuretic Use in Patients With Heart Failure and Reduced Ejection Fraction in DAPA-HF. Circulation. 2020;142(11):1040-54. doi: 10.1161/CIRCULATIONAHA.120.047077.

44. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019;381(21):1995-2008. doi: 10.1056/NEJMoa1911303.

45. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. 2020;383(15):1413-24. doi: 10.1056/NEJMoa2022190.

46. Bocchi EA, Biolo A, Moura LZ, Figueiredo Neto JA, Montenegro CEL, Albuquerque DC. Emerging Topics in Heart Failure: Sodium-Glucose Co-Transporter 2 Inhibitors (SGLT2i) in HF. Arq Bras Cardiol. 2021;116(2):355-8. doi: 10.36660/abc.20210031.

47. Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, et al. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. N Engl J Med. 2021;384(2):117-28. doi: 10.1056/NEJMoa2030183.

48. Konstam MA, Gheorghiade M, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, et al. Effects of Oral Tolvaptan in Patients Hospitalized for Worsening Heart Failure: The EVEREST Outcome Trial. JAMA. 2007;297(12):1319-31. doi: 10.1001/jama.297.12.1319.

49. Konstam MA, Kiernan M, Chandler A, Dhingra R, Mody FV, Eisen H, et al. Short-Term Effects of Tolvaptan in Patients with Acute Heart Failure and Volume Overload. J Am Coll Cardiol. 2017;69(11):1409-19. doi: 10.1016/j.jacc.2016.12.035.

50. Felker GM, Mentz RJ, Cole RT, Adams KF, Egnaczyk GF, Fiuzat M, et al. Efficacy and Safety of Tolvaptan in Patients Hospitalized with Acute Heart Failure. J Am Coll Cardiol. 2017;69(11):1399-406. doi: 10.1016/j.jacc.2016.09.004.

51. Ter Maaten JM, Rao VS, Hanberg JS, Wilson FP, Bellumkonda L, Assefa M, et al. Renal Tubular Resistance is the Primary Driver for Loop Diuretic Resistance in Acute Heart Failure. Eur J Heart Fail. 2017;19(8):1014-22. doi: 10.1002/ejhf.757.

52. Michaud CJ, Mintus KC. Intravenous Chlorothiazide Versus Enteral Metolazone to Augment Loop Diuretic Therapy in the Intensive Care Unit. Ann Pharmacother. 2017;51(4):286-92. doi: 10.1177/1060028016683971.

53. Liu C, Peng Z, Gao X, Gajic O, Dong Y, Prokop LJ, et al. Simultaneous Use of Hypertonic Saline and IV Furosemide for Fluid Overload: A Systematic Review and Meta-Analysis. Crit Care Med. 2021;49(11):1163-75. doi: 10.1097/CCM.0000000000005174.

54. Hanberg JS, Rao V, Ter Maaten JM, Laur O, Brisco MA, Wilson FP, et al. Hypochloremia and Diuretic Resistance in Heart Failure: Mechanistic Insights. Circ Heart Fail. 2016;9(8):10.1161/CIRCHEARTFAILURE.116.003180 e003180. doi: 10.1161/CIRCHEARTFAILURE.116.003180.

55. Paterna S, Fasullo S, Parrinello G, Cannizzaro S, Basile I, Vitrano G, et al. Short-Term Effects of hypertonic Saline Solution in Acute Heart Failure and Long-Term Effects of a Moderate Sodium Restriction in Patients with Compensated Heart Failure with New York Heart Association class III (Class C) (SMAC-HF Study). Am J Med Sci. 2011;342(1):27-37. doi: 10.1097/MAJ.0b013e31820f10ad.

56. Agostoni P, Marenzi G, Lauri G, Perego G, Schianni M, Sganzerla P, et al. Sustained Improvement in Functional Capacity After Removal of Body Fluid with Isolated Ultrafiltration in Chronic Cardiac Insufficiency: Failure of Furosemide to Provide the Same Result. Am J Med. 1994;96(3):191-9. doi: 10.1016/0002-9343(94)90142-2.

57. Costanzo MR, Saltzberg MT, Jessup M, Teerlink JR, Sobotka PA, et al. Ultrafiltration is Associated with Fewer Rehospitalizations than Continuous Diuretic Infusion in Patients with Decompensated Heart Failure: Results from UNLOAD. J Card Fail. 2010;16(4):277-84. doi: 10.1016/j.cardfail.2009.12.009.

58. Bart BA, Goldsmith SR, Lee KL, Givertz MM, O'Connor CM, Bull DA, et al. Ultrafiltration in Decompensated Heart Failure with Cardiorenal Syndrome. N Engl J Med. 2012;367(24):2296-304. doi: 10.1056/NEJMoa1210357.

59. Costanzo MR, Ronco C, Abraham WT, Agostoni P, Barasch J, Fonarow GC, et al. Extracorporeal Ultrafiltration for Fluid Overload in Heart Failure: Current Status and Prospects for Further Research. J Am Coll Cardiol. 2017;69(19):2428-45. doi: 10.1016/j.jacc.2017.03.528.

Diuretics In Stable Outpatients with Mild Heart Failure – May I Discontinue Them?

Marciane Maria Rover,[1,2] Aline Coletto Jaccottet,[1] Diether Villegas Calle,[1] Roberto Tofani Sant´Anna[1,3]

Instituto de Cardiologia - Fundação Universitária de Cardiologia,[1] Porto Alegre, RS – Brazil

Núcleo de Insuficiência Cardíaca e Cardiomiopatias do Serviço de Cardiologia do Hospital Moinhos de Vento,[2] Porto Alegre, RS – Brazil

Université de Montreal,[3] Quebec – Montreal

Heart failure: congestion and diuretic therapy

Congestion is a key component of the pathophysiology of heart failure (HF) and causes some of the cardinal symptoms of the disease, such as edema, orthopnea, and dyspnea on exertion. Congestion management is, therefore, of utmost importance for a successful HF treatment. Management is based on the prescription of loop diuretics for symptomatic patients according to different guidelines, although there are no placebo-controlled studies that support their use for reducing mortality.[1,2] When they are administered alone or in combination with other drugs, diuretics improve functional capacity and quality-of-life scores by reducing preload, ventricular filling pressures, and mitral regurgitation, resulting in increased cardiac output.[3]

Congestion assessment is essential in diuretic optimization. Within this context, we should consider the low accuracy of clinical signs of congestion, especially when these signs are used alone.[4] Conversely, concomitant assessment of several factors – including New York Heart Association (NYHA) functional class, orthopnea or paroxysmal nocturnal dyspnea, edema, pulmonary rales, third heart sound, hepatojugular reflux, and jugular venous distension – can identify patients at higher risk when they are grouped together by congestion scores.[5] Additional tests increase predictive value and contribute to decision-making. The most common methods are serum natriuretic peptide measurement and imaging tests such as chest radiography, lung ultrasound, and echocardiography. They may be considered before diuretic discontinuation and for monitoring blood volume, especially in doubtful cases.

Loop diuretics are potentially associated with electrolyte disturbances, worsening renal function, and hypovolemia, causing hypotension and limiting the adjustment of disease-modifying drugs (DMDs).[6] Thus, the optimal dose of loop diuretics in HF should be the minimum dose capable of keeping the patient euvolemic. In Table 1, the mechanisms of action, indications, and adverse effects of different diuretic drugs are specified. The discussion herein is essentially about the discontinuation of loop diuretics when they have already fulfilled their role and become potentially harmful, since, in addition to various adverse effects, they may also limit the therapeutic optimization of drugs that will in fact impact the natural history of HF and patient survival.

Observational data suggest that high-dose diuretics are associated with poor clinical outcomes.[7] Eshaghian et al. evaluated a cohort of 1,354 patients and demonstrated, even after adjusting for all other disease severity factors, a strong and independent association of high-dose furosemide with worsening survival.[8] Dini et al. also evaluated a cohort and identified a threshold furosemide dose of 50 mg/day as a predictor of 3-year mortality regardless of renal function, left ventricular filling pattern on echocardiography, and background therapy.[9] Coiro et al.[10] used a patient sample from the EMPHASIS-HF study and demonstrated that the use of loop diuretics is a prognostic factor in HF with reduced ejection fraction (HFrEF) with an impact comparable to traditional markers, such as recent hospitalization and B-type natriuretic peptide. Higher doses lead to a higher risk.[10]

Conversely, the prescription of high-dose diuretics is linked to more advanced HF, as shown by Pellicori et al.[11] Therefore, the need for diuretics would be the factor that is associated with a higher risk, not their potential deleterious effects. We should also consider that not prescribing diuretics or prescribing suboptimal doses would lead to residual congestion, especially in the period following hospitalization for acute HF, and this is associated with poor outcomes.[12] Thus, the safety and benefit of diuretic discontinuation in patients with HFrEF will only be determined by placebo-controlled, randomized clinical trials.

Compensated heart failure: safety of diuretic discontinuation – ReBIC-1 (Figure)[13]

Furosemide is commonly prescribed for symptomatic relief in patients with chronic HF, although few studies have provided robust data on the benefit of diuretics in compensated patients with mild symptoms and in a euvolemic state. Until the publication of the ReBIC-1 study in 2019, there was tremendous concern about the safety and tolerability of furosemide withdrawal in stable patients. This prospective, double-blind, randomized study included 188 patients with left ventricular ejection fraction (LVEF) < 45% for diuretic discontinuation or standard treatment. Inclusion criteria were being on low-dose furosemide (40 to 80 mg), no visits or hospitalizations in the past 6 months, being stable and NYHA class I or II, and receiving optimal therapy with DMD.[13] Patients with clinical congestion, based on a clinical congestion score > 5 points,[5] were excluded. Primary endpoints were

Keywords

Heart Failure; Diuretics; Furosemide.

Mailing Address: Marciane Maria Rover •
Instituto de cardiologia - Equipe IC avançada e transplante cardíaco - Av. Princesa Isabel, 395, sala 105. Postal Code 90620-001, Porto Alegre, RS - Brazil
E-mail: rovermm@gmail.com

Manuscript received February 01, 2022, revised manuscript February 09, 2022, accepted February 24, 2022

DOI: https://doi.org/10.36660/abchf.20220019

Table 1 – Diuretics: mechanism of actions, indications, and potential side effects

	Mechanism of action	Effect on mortality	Indication	Side effects
Loop diuretic	Reduces sodium reabsorption in the thick ascending limb of the loop of Henle by inhibiting the Na-K-Cl^{-2} transporter.	No	Congestion management	Allergic and hypersensitivity reactions such as rash, electrolyte disturbances (hypokalemia, metabolic alkalosis), hyperuricemia, interstitial nephritis, and ototoxicity
Thiazide diuretic	Primarily inhibits sodium transport in the distal convoluted tubule.	No	Refractory congestion management	Hyponatremia, hypokalemia, elevated plasma glucose and cholesterol concentrations and magnesium depletion, hyperuricemia, hypercalciuria, and increased risk of kidney stones
Mineralocorticoid receptor antagonist	Acts on the principal cells of the collecting tubules. Reabsorption of cationic sodium without an anion creates a negative electrical gradient into the lumen, which favors secretion of potassium and hydrogen ions.	Yes	Patients with HFrEF (≤35%) who remain symptomatic despite optimal initial drug therapy	Hyperkalemia and endocrine effects (gynecomastia, breast pain, menstrual irregularities, impotence, and decreased libido)
SGLT2i	Inhibits the effects of the sodium-glucose cotransporter 2, which promotes osmotic diuresis and natriuresis, and may reduce preload and, through effects on the endothelium, promote vasodilatation and consequently reduce afterload.	Yes	Patients with HFrEF, with or without T2D, in combination with optimized treatment	Genitourinary infections, reduced bone mineral density, ulcerations with risk of amputation, and increased predisposition to diabetic ketoacidosis

T2D: type 2 diabetes; HFrEF: heart failure with reduced ejection fraction; SGLT2i: sodium-glucose cotransporter 2 inhibitor.

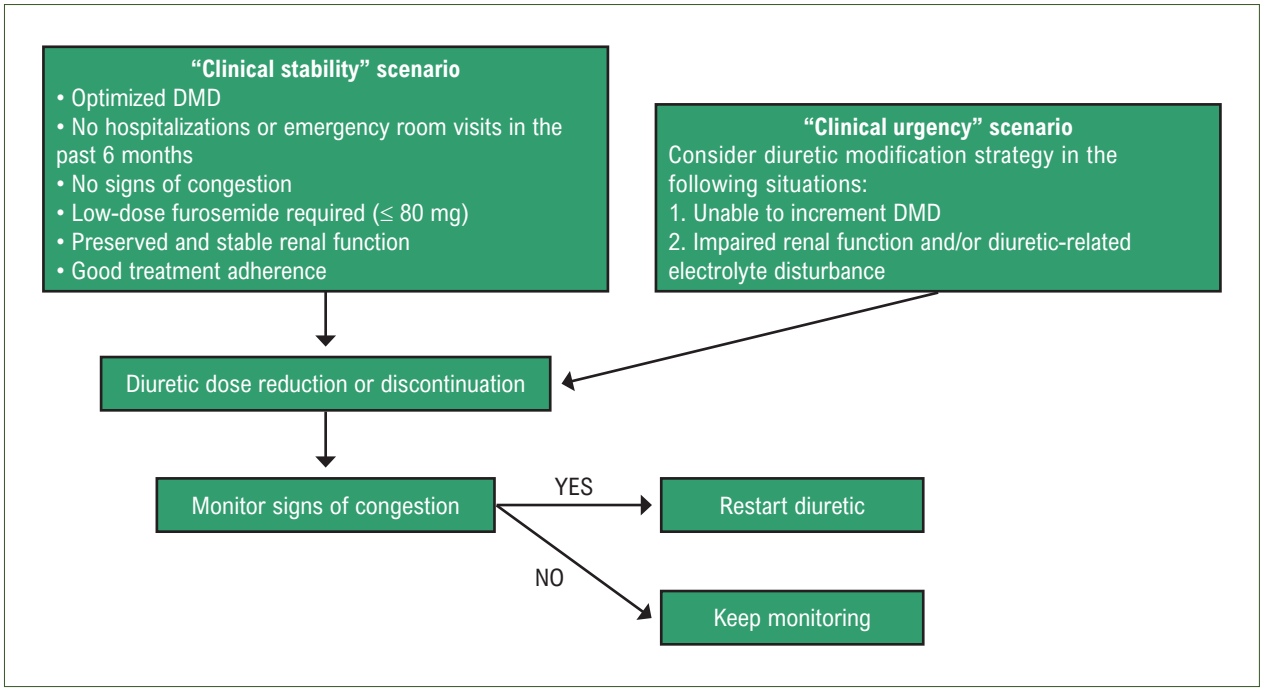


Figure 1 – *Suggested flowchart for using loop diuretics in patients with HFrEF. DMD: disease-modifying drug; HFrEF: heart failure with reduced ejection fraction.*

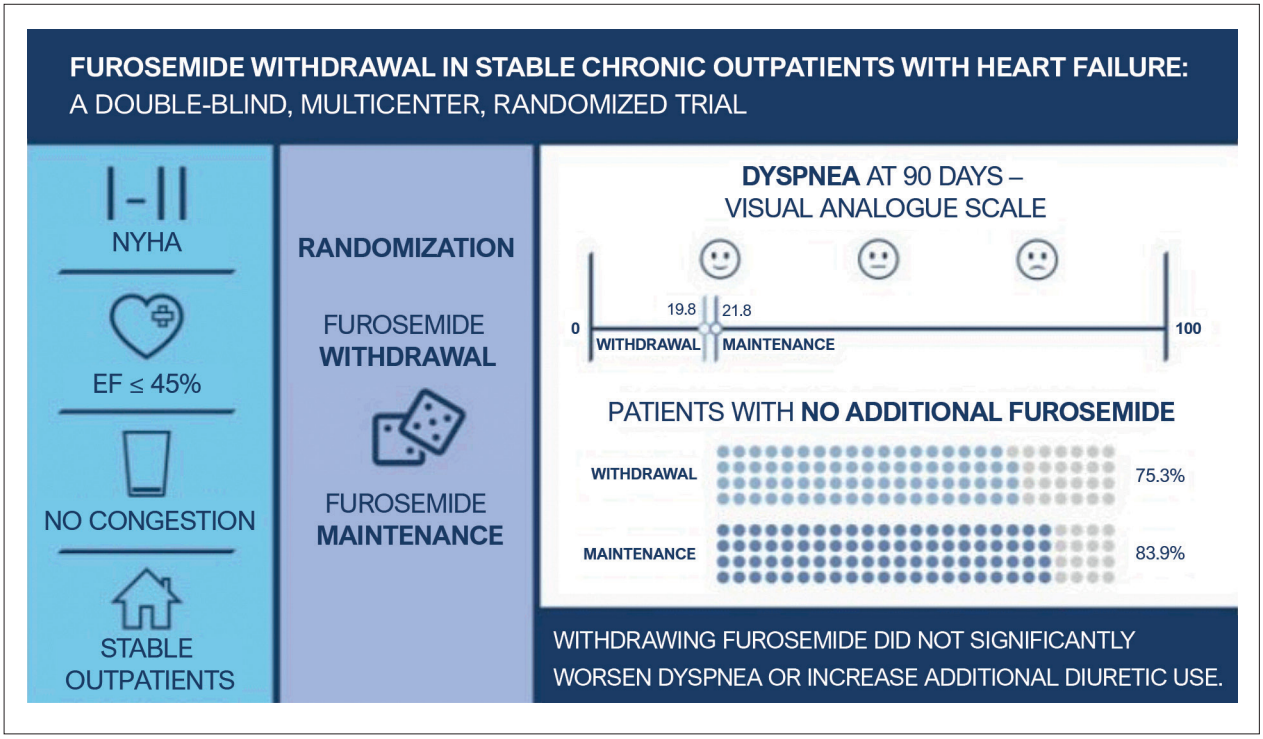


Figure 2 – *Stable chronic outpatients with HF and mild symptoms were randomized to furosemide maintenance or withdrawal – a double-blind, placebo-controlled trial showed no significant change in self-reported dyspnea or increase in the need to reuse furosemide when the groups were compared.*

symptoms measured by a visual analog scale for dyspnea and the proportion of patients maintained without diuretics over the 90-day follow-up period.

Regarding the results, there was no significant difference between the two intervention groups (furosemide maintenance vs. withdrawal) for the co-primary endpoint of patient-reported dyspnea assessed on a visual analog scale ($p = 0.94$). Similarly, no statistically significant difference was observed in the percentage of patients who needed to reuse loop diuretics ($p = 0.16$). The risk of reusing diuretics in the withdrawal group was 1.69 with a wide confidence interval, suggesting statistical uncertainty in the assessment of this endpoint. Patients were followed-up for a short period, during which there was no difference in clinical outcomes between the groups. Because it was a placebo-controlled, randomized clinical trial that evaluated loop diuretic withdrawal, ReBIC-1 can be considered a great contribution to decision-making regarding the safety of discontinuing furosemide in stable patients with chronic disease.

The study had limitations of sample size and follow-up duration, which preclude a conclusion about the effect that diuretic discontinuation would eventually have on the risk of hospitalization and death. Also, as the study was conducted between October 2015 and August 2018, treatment with sodium-glucose cotransporter 2 (SGTL2) inhibitors was not routinely established. DAPA-HF was published in 2019 and showed a 26% reduction in the primary outcome of cardiovascular death or worsening HF, which was significantly lower in the dapagliflozin group.[14] EMPEROR-Reduced evaluated empagliflozin in 3,730 patients with HFrEF, 50.2% of whom had type 2 diabetes. There was a 25% reduction in the primary outcome of cardiovascular death or hospitalization for HF in favor of empagliflozin.[15] These data confirm the results of DAPA-HF and support the rationale for using SGLT2 inhibitors in patients with HFrEF to attenuate symptoms, improve quality of life, and reduce the risk of hospitalization and cardiovascular death. This class may be used to keep patients euvolemic with DMD. Thus, the decision to reduce or discontinue loop diuretics becomes easier and safer in stable patients without congestion in the face of another drug with a diuretic effect that directly reduces cardiovascular events and hospitalizations for HF.

Optimizing blood volume can facilitate the introduction and achievement of the target DMD dose.[16] Reduced diuretic use may decrease hypotension due to initiation of sacubitril-valsartan. In patients with HFrEF, both systolic blood pressure (SBP) and pulse pressure depend primarily on left ventricular stroke volume, while blood pressure and diastolic blood pressure vary according to total blood volume and degree of vasodilatation.[17] Both components are affected by the treatment used in HFrEF. Escalation to target DMD dose may be limited by the presence of hypotension. SBP < 90 mm Hg is an established marker of poor prognosis in acute HF.[18] However, its implications in chronic HF are more complex. SBP is a component of prognostic scores (eg, Seattle model) but does not

necessarily have a causal relationship with adverse events. Patients with lower blood pressure obtain similar benefits from treatment with sacubitril-valsartan and carvedilol compared to patients with higher blood pressure.[19,20]

Conclusion: when to discontinue loop diuretics?

In view of the evidence discussed and considered above, loop diuretics play a crucial role in patients with decompensated HF and signs of congestion. In stable patients with compensated chronic disease, it is increasingly necessary that diuretic use is reduced to make room for therapeutic optimization of drugs that impact the natural history of HF. Hypotension is common in this group of patients and becomes a limiting factor for dose increments. In this setting, the first step should be to reduce or discontinue medications that are not the mainstays of HF treatment, such as calcium channel blockers and alpha-blockers. If symptoms of hypotension persist, the diuretic should be adjusted and even discontinued in euvolemic patients.[17] Importantly, it is essential to monitor these patients frequently and pay attention to signs of congestion and the need to restart the diuretic.

Another specific situation consists of patients with recovered ejection fraction, either through the action of DMD, natural recovery from a condition (eg, myocarditis), or the effect of cardiac resynchronization.[21-23] It is believed that LVEF can be recovered in approximately half of patients.[23] In such cases, DMDs should be maintained as tolerated, and diuretics may be discontinued provided that no associated conditions require their maintenance.

Future randomized studies that evaluate diuretic discontinuation in patients receiving contemporary therapy for HF, including sacubitril-valsartan and SGLT2 inhibitors, and have reduced clinical events as an outcome will be able to solidify the recommendations.

Acknowledgments

We are grateful to Dr Luis E. Rohde for mentoring and conducting the ReBIC-1 trial, which was a landmark trial for the safety of discontinuing furosemide in stable patients with compensated heart failure. We are also grateful for the partnership and opportunity to participate in the study as well as for the unconditional support to research.

Author Contributions

Conception and design of the research: Rover MM, Jaccottet AC, Sant´Anna RT; Writing of the manuscript and Critical revision of the manuscript for intellectual contente: Rover MM, Jaccottet AC, Calle DV, Sant´Anna RT.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Rohde LEP, Montera MW, Bocchi EA, Clausell NO, Albuquerque DC, Rassi S, et al. Diretriz Brasileira de Insuficiência Cardíaca Crônica e Aguda. Arq Bras Cardiol. 2018;111(3):436-539. doi: 10.5935/abc.20180190.
2. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure: Developed by the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC). With the Special Contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2022;24(1):4-131. doi: 10.1002/ejhf.2333.
3. Anand IS, Florea VG. Diuretics in chronic heart failure – benefits and hazards. Eur Heart J 2001;3(Suppl):1-18.
4. Girerd N, Seronde MF, Coiro S, Chouihed T, Bilbault P, Braun F, et al. Integrative Assessment of Congestion in Heart Failure Throughout the Patient Journey. JACC Heart Fail. 2018;6(4):273-85. doi: 10.1016/j.jchf.2017.09.023.
5. Rohde LE, Silva LB, Goldraich L, Grazziotin TC, Palombini DV, Polanczyk CA, et al. Reliability and Prognostic Value of Traditional Signs and Symptoms in Outpatients with Congestive Heart Failure. Can J Cardiol. 2004;20(7):697-702.
6. Opie LH, Gersh BJ. Drugs for the Heart. 8th ed. Amsterdam, Elsevier; 2012.
7. Rosa PR, Rohde LE, Doebber M, Ribeiro ALP, Prado DP, Bertoldi EG, et al. Rational and Design of a Randomized, Double-Blind, Multicenter Trial to Evaluate the Safety and Tolerability of Furosemide Withdrawal in Stable Chronic Outpatients with Heart Failure: The ReBIC-1 Trial. Am Heart J. 2017;194:125-31. doi: 10.1016/j.ahj.2017.08.012.
8. Eshaghian S, Horwich TB, Fonarow GC. Relation of Loop Diuretic Dose to Mortality in Advanced Heart Failure. Am J Cardiol. 2006;97(12):1759-64. doi: 10.1016/j.amjcard.2005.12.072.
9. Dini FL, Ghio S, Klersy C, Rossi A, Simioniuc A, Scelsi L, et al. Effects on Survival of Loop Diuretic Dosing in Ambulatory Patients with Chronic Heart Failure Using a Propensity Score Analysis. Int J Clin Pract. 2013;67(7):656-64. doi: 10.1111/ijcp.12144.
10. Coiro S, Girerd N, McMurray JJV, Pitt B, Swedberg K, van Veldhuisen DJ, et al. Diuretic Therapy as Prognostic Enrichment Factor for Clinical Trials in Patients with Heart Failure with Reduced Ejection Fraction. Clin Res Cardiol. 2021;110(8):1308-20. doi: 10.1007/s00392-021-01851-w.
11. Pellicori P, Cleland JG, Zhang J, Kallvikbacka-Bennett A, Urbinati A, Shah P, et al. Cardiac Dysfunction, Congestion and Loop Diuretics: Their Relationship to Prognosis in Heart Failure. Cardiovasc Drugs Ther. 2016;30(6):599-609. doi: 10.1007/s10557-016-6697-7.

12. Rubio-Gracia J, Demissei BG, Ter Maaten JM, Cleland JG, O'Connor CM, Metra M, et al. Prevalence, Predictors and Clinical Outcome of Residual Congestion in Acute Decompensated Heart Failure. Int J Cardiol. 2018;258:185-91. doi: 10.1016/j.ijcard.2018.01.067.

13. Rohde LE, Rover MM, Figueiredo Neto JA, Danzmann LC, Bertoldi EG, Simões MV, et al. Short-Term Diuretic Withdrawal in Stable Outpatients with Mild Heart Failure and no Fluid Retention Receiving Optimal Therapy: A Double-Blind, Multicentre, Randomized Trial. Eur Heart J. 2019;40(44):3605-12. doi: 10.1093/eurheartj/ehz554.

14. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019;381(21):1995-2008. doi: 10.1056/NEJMoa1911303.

15. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. 2020 8;383(15):1413-24. doi: 10.1056/NEJMoa2022190.

16. Felker GM. Must I keep taking all these medicines? Optimizing diuretics in chronic heart failure. Eur Heart J. 2019;40(44):3613-15. doi: 10.1093/eurheartj/ehz679.

17. Cautela J, Tartiere JM, Cohen-Solal A, Bellemain-Appaix A, Theron A, Tibi T, et al. Management of Low Blood Pressure in Ambulatory Heart Failure with Reduced Ejection Fraction Patients. Eur J Heart Fail. 2020;22(8):1357-65. doi: 10.1002/ejhf.1835.

18. Ambrosy AP, Vaduganathan M, Mentz RJ, Greene SJ, Subačius H, Konstam MA, et al. Clinical Profile and Prognostic Value of Low Systolic Blood Pressure in Patients Hospitalized for Heart Failure with Reduced Ejection Fraction: Insights from the Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan (EVEREST) trial. Am Heart J. 2013;165(2):216-25. doi: 10.1016/j.ahj.2012.11.004.

19. Böhm M, Young R, Jhund PS, Solomon SD, Gong J, Lefkowitz MP, et al. Systolic Blood Pressure, Cardiovascular Outcomes and Efficacy and Safety of Sacubitril/Valsartan (LCZ696) in Patients with Chronic Heart Failure and Reduced Ejection Fraction: Results from PARADIGM-HF. Eur Heart J. 2017;38(15):1132-43. doi: 10.1093/eurheartj/ehw570.

20. Rouleau JL, Roecker EB, Tendera M, Mohacsi P, Krum H, Katus HA, et al. Influence of Pretreatment Systolic Blood Pressure on the Effect of Carvedilol in Patients with Severe Chronic Heart Failure: The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study. J Am Coll Cardiol. 2004;43(8):1423-9. doi: 10.1016/j.jacc.2003.11.037.

21. Nijst P, Martens P, Dauw J, Tang WHW, Bertrand PB, Penders J, et al. Withdrawal of Neurohumoral Blockade After Cardiac Resynchronization Therapy. J Am Coll Cardiol. 2020;75(12):1426-38. doi: 10.1016/j.jacc.2020.01.040.

22. Tschöpe C, Cooper LT, Torre-Amione G, Van Linthout S. Management of Myocarditis-Related Cardiomyopathy in Adults. Circ Res. 2019;124(11):1568-83. doi: 10.1161/CIRCRESAHA.118.313578.

23. Wilcox JE, Fang JC, Margulies KB, Mann DL. Heart Failure with Recovered Left Ventricular Ejection Fraction: JACC Scientific Expert Panel. J Am Coll Cardiol. 2020;76(6):719-34. doi: 10.1016/j.jacc.2020.05.075.

Review Article

Pharmacological Primary Prevention of Chemotherapy-Induced Cardiomyopathy: What is the Best Approach?

Mônica Samuel Avila,[1] *Deborah de Sá Pereira Belfort,*[1] *Mauro Rogério de Barros Wanderley Júnior*[2]

Departamento de Transplante Cardíaco – Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo,[1] *São Paulo, SP – Brazil*

Departamento de Transplante Cardíaco – Santa Casa Campo Grande,[2] *Campo Grande, MS – Brazil*

Introduction

Advances in oncology, such as better access to health care system, earlier cancer diagnosis, and new chemotherapies, have led to longer survival of oncologic patients over the last decades.[1] However, this population is vulnerable to cardiovascular drug-related adverse events like cardiomyopathy, which leads to heart failure and impairs survival and quality of life.[2,3] Among different classes of chemotherapeutic agents, anthracyclines (ANT) stand out as the most related to cardiomyopathy, which may affect cancer survivors in 9% of all cases.[4]

The most widely recognized definition of cardiotoxicity is based on changes in left ventricular ejection fraction (LVEF).[5] A decline of 10% to a value below 50% or a decline associated with heart failure symptoms during or after the use of a cardiotoxic agent suggests cardiotoxicity.[2]

Once chemotherapy-induced cardiomyopathy is present, prompt heart failure treatment should be started with neurohormonal antagonists, such as angiotensin converting enzyme inhibitor (ACEI), angiotensin receptor blockers (ARB), and betablockers. Despite contemporary heart failure treatment, up to 89% of patients with ANT-induced cardiotoxicity do not experience complete recovery.[6,7] In order to avoid decreasing LVEF and exposing patients to the risk of irreversible cardiac dysfunction even with heart failure treatment, prevention of chemotherapy-induced cardiotoxicity has been the focus of research in the last years.

Monitorization of cardiotoxicity

The frequency of cardiovascular evaluation in monitorization of cardiotoxicity depends on both individual cardiovascular risk, which involves individual risk factors, and intrinsic chemotherapy risk. The following are known risk factors for cardiotoxicity: female sex; age below 18 years or over 65 years; comorbidities like systemic arterial hypertension or other previous cardiovascular disease, diabetes, obesity, or renal insufficiency; high ANT cumulative dose; chemotherapy association, especially trastuzumab and ANT; genetic alterations such as trisomy 21; hemochromatosis; and mediastinal radiotherapy (Table 1).[8,9] The incidence of cardiovascular events during the 10 days following ANT administration is less than 2% in the low-risk group and more than 5% in the high-risk group, leading to different protocols based on individual risk.[10]

A position paper of the European Society of Cardiology[12] suggests monitorization using echocardiogram (including global longitudinal strain [GLS] and 3D LVEF) and biomarkers in order to identify subclinical markers of cardiotoxicity and consider cardioprotective medications. The frequency of evaluation depends on individual risk considering individual and chemotherapy factors. Figures 1 and 2 show the European Society of Cardiology protocol for ANT and trastuzumab, respectively.

The Brazilian Cardio-oncology guideline[13] suggests a slightly different approach (Figures 3 and 4). Different intervals are also used depending on baseline LVEF. For ANT, if baseline LVEF is > 55%, only echocardiogram is recommended after 3, 6, and 12 months. If LVEF is between 50% and 55%, in addition to echocardiogram, troponin and natriuretic peptides analysis is also recommended < 72 hours after exposure to ANT. If LVEF is < 50%, prompt heart failure treatment should be initiated and first image evaluation should be made after 45 days. For trastuzumab, if LVEF is > 55%, echocardiogram should be done after 12 and 24 weeks and at the end of treatment. If LVEF is between 50% and 55%, in addition to echocardiogram, troponin and natriuretic peptides analysis is also recommended < 72 hours after exposure. If LVEF is < 50%, prompt heart failure treatment should be initiated and first image evaluation should be made after 12 weeks and 18 weeks and at the end of treatment.

Subclinical cardiotoxicity markers

The actual definition of cardiotoxicity, although largely used in different trials, raises some concern, since LVEF reduction may represent a late stage of myocardial injury and, therefore, it only allows diagnosis in a point where full recovery is less likely. In order to improve detection of cardiotoxicity, there is a growing body of evidence on the use of elevated biomarkers[14] and myocardial strain reduction[15] as subclinical cardiotoxicity markers, although there is not yet any formal recommendation for treatment based on them.

Troponin is a complex of three regulatory proteins (troponin C, troponin I, and troponin T) that are integral to muscle

Keywords

Cardiotoxicity; Heart Failure; Pharmaceutical Preparations; Primary Prevention.

Mailing Address: Mônica Samuel Avila •
Rua Dr. Enéas de Carvalho Aguiar, 44. Postal Code 05403-900, São Paulo, SP – Brazil
Email: mo_avila@hotmail.com
Manuscript received January 24, 2022, revised manuscript February 01, 2022, accepted February 25, 2022

DOI: https://doi.org/10.36660/abchf.20220020

Table 1 - Assessment of cardiotoxicity risk

Therapy-related factors	Patient-related factors
Low risk of cardiotoxicity	
Lower dose ANT (e.g. doxorubicin < 200 mg/m^2, epirubicin < 300 mg/m^2), lipossomal formulations	Age > 18 and < 50 years
Trastuzumab without ANT	
Medium risk of cardiotoxicity	
Modest-dose ANT (doxorubicin 200 to 400 mg/m^2 or epirubicin 300 to 600 mg/m^2)	Age 50 to 64 years 1 to 2 CV risk factors such as hypertension, dyslipidemia, obesity, insulin resistance, smoking
ANT followed by trastuzumab	
VEGF tyrosine kinase inhibitors	
Second- and third-generation Bcr-Abl tyrosine kinase inhibitors	
Proteasome inhibitors	
Combination imune checkpoint inhibitors	
High risk of cardiotoxicity	
Simultaneous ANT and trastuzumab	Age ≥ 65 years > 2 CV risk factors such as hypertension, dyslipidemia, obesity, insulin resistance, smoking Diabetes Underlying CV disease: CAD, PAD, CMP, severe VHD, heart failure Reduced or low-normal LVEF (50% to 54%) pre-treatment Prior cancer therapy
High-dose ANT (doxorubicin ≥ 400 mg/m^2 or epirubicin ≥ 600 mg/m^2)	
Modest-dose ANT plus left chest radiation therapy	
Elevated cardiac troponin post-ANT prior to HER2-targeted therapy	
High-dose radiation therapy to central chest including heart in radiation field ≥ 30 Gy	
VEGF tyrosine kinase inhibitors following previous ANT chemotherapy	

ANT: anthracycline; Bcr, breakpoint cluster region; CAD, coronary artery disease; CMP, cardiomyopathy; CV, cardiovascular; HER2: human epidermal growth factor receptor 2; LVEF: left ventricular ejection fraction; PAD: peripheral artery disease; VEGF: vascular endothelial growth factor; VHD: valvular heart disease. Adapted from Celutkiene et al.[11]

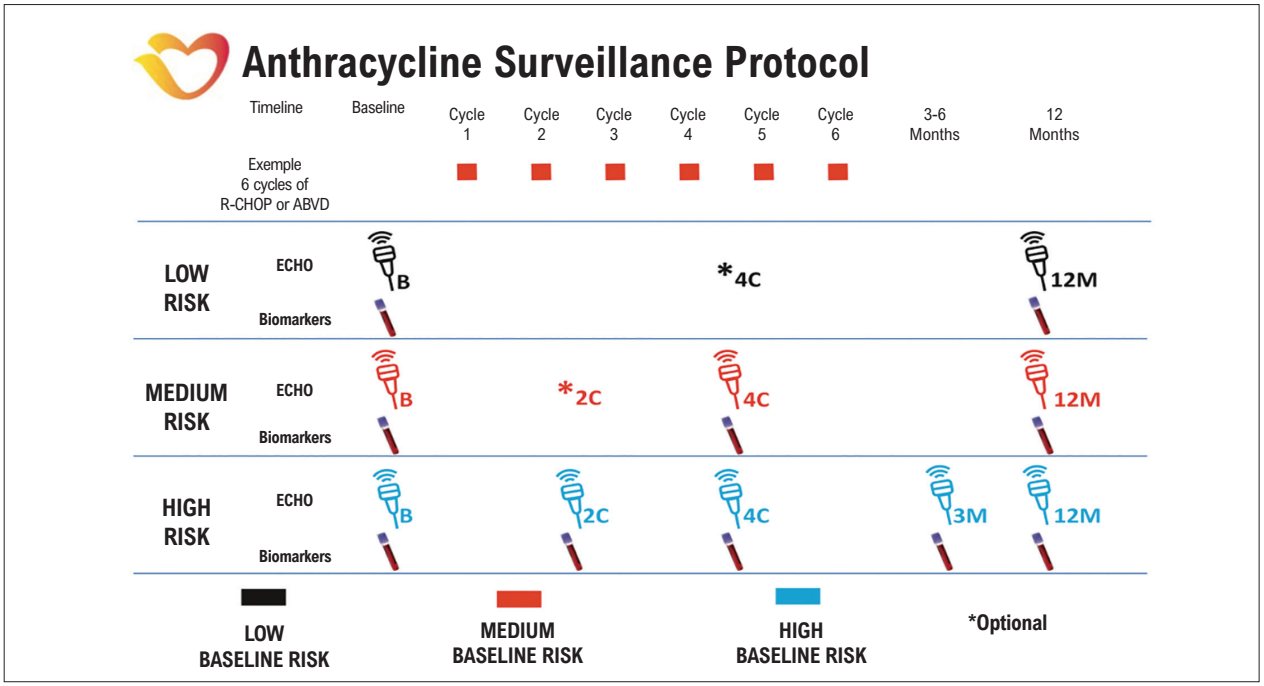


Figure 1 – *A surveillance pathway using biomarkers and echocardiography for cancer patients receiving six cycles of anthracycline chemotherapy with timing based upon baseline cardiovascular risk. Pathways for low risk, medium risk and high risk are presented. ABVD, doxorubicin, bleomycin, vinblastine; B, baseline pre-treatment; C, cycle of chemotherapy; M, months post-final cycle; R-CHOP, Cyclosphosphamide, doxorubicin, vincristine, prednisone with rituximab. *Optional additional assessment timepoints.*

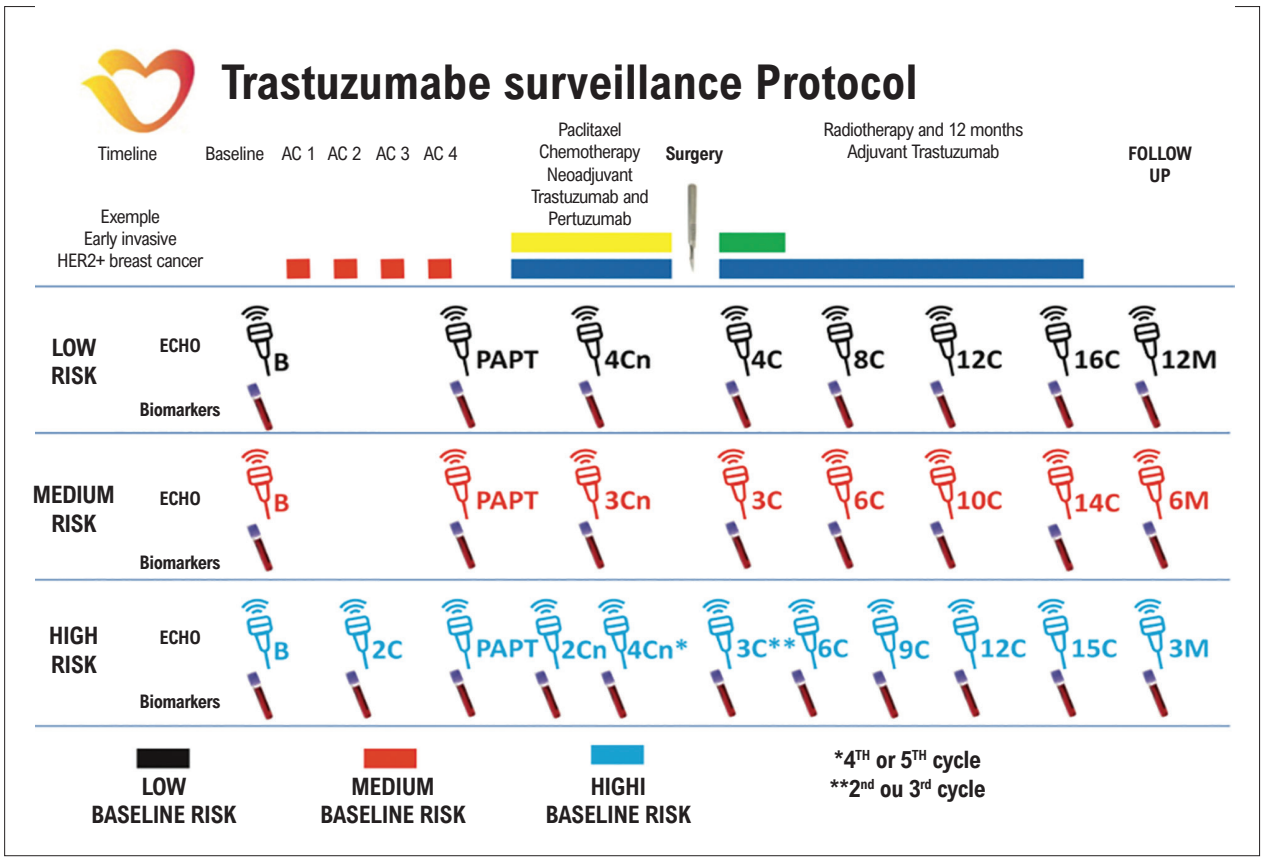


Figure 2 – *A suveveilance pathway using biomarkers and echocardiography for patients receiving neoadjuvant anthracycline (AC) chemotherapy (doxorubicin or epirubicin) and tratuzumab followed by 12 months of adjuvant tratuzumab for HER2+ early breast cancer with timing based upon baseline cardiovascular risk. Pathways for low risk, medium risk and high risk are presented. B, baseline pre-treatment; C, Chemotherapy or adjuvant trastuzumab; Cn, neoadjuvant cycle of tratuzubab; M, months post-fina cycle; PAPT, post-anthracycline chemotherapy pre-trastuzumab. *, **Optional additional assessment timepoints.*

contraction in skeletal muscle and cardiac muscle. Prolonged ischemia, trauma, inflammation, or cardiotoxic agents may result in injury of cardiac cells. This injury is accompanied by the destruction of cell membranes and organelles and the release of troponin and other proteins into the blood.[16] These proteins are the most studied biomarker in subclinical ANT-induced cardiotoxicity.[14]

Cardiac troponin I (cTnI) elevation was described in one third of patients after high-dose ANT,[15,17] and the degree of cTnI elevation was associated with the cumulative dose of ANT.[18] This biomarker is also associated with the degree of left ventricular dysfunction. In one cohort, patients with cTnI level over 0.5 ng/mL presented significant and persistent LVEF reduction, while patients with transient LVEF decrease had cTnI levels below 0.5 ng/Ml.[19] In another study, cTnI values persisting > 0.08 ng/mL over a month after therapy were associated with 84% risk of cardiotoxicity, while cTnI below the reference range was associated with 1% risk.[17]

In addition to troponins, other biomarkers have been studied in subclinical cardiotoxicity. Natriuretic peptides have controversial correlation with cardiotoxicity in the literature. Some evidence suggests an association between NT-proBNP level and cumulative dose of ANT.[20,21] However, in two cohorts, while troponin predicted cardiac toxicity, natriuretic peptides did not.[22,23] Markers of inflammation and endothelial dysfunction are also targets of research,[14] but they are less used in clinical practice.

Early identification of subclinical left ventricular dysfunction is also possible using GLS, which is an evaluation of two-dimensional speckle-tracking that allows for study of global and regional myocardial deformation to detect subtle alterations in systolic function, particularly related to ANT chemotherapy.[24] Evidence including a metanalysis of 21 studies and 1782 patients with cancer suggests that GLS can identify subclinical myocardial dysfunction, and it also has prognostic implication regarding chemotherapy-induced cardiotoxicity or heart failure.[15] The use of GLS could identify patients with higher risk of cardiotoxicity and improve cardiac surveillance.

Following this rationale, the SUCCOUR Trial evaluated a GLS-based-approach to initiation of cardioprotection compared to standard care, to reduce the risk of future LVEF reduction, interruption of cancer therapy or cancer therapy-related cardiac dysfunction.[25] ANT-exposed patients with another risk factor for heart failure were enrolled to start cardioprotection with ACEI and betablocker after 10% reduction in LVEF to less than 55% or 5% reduction with

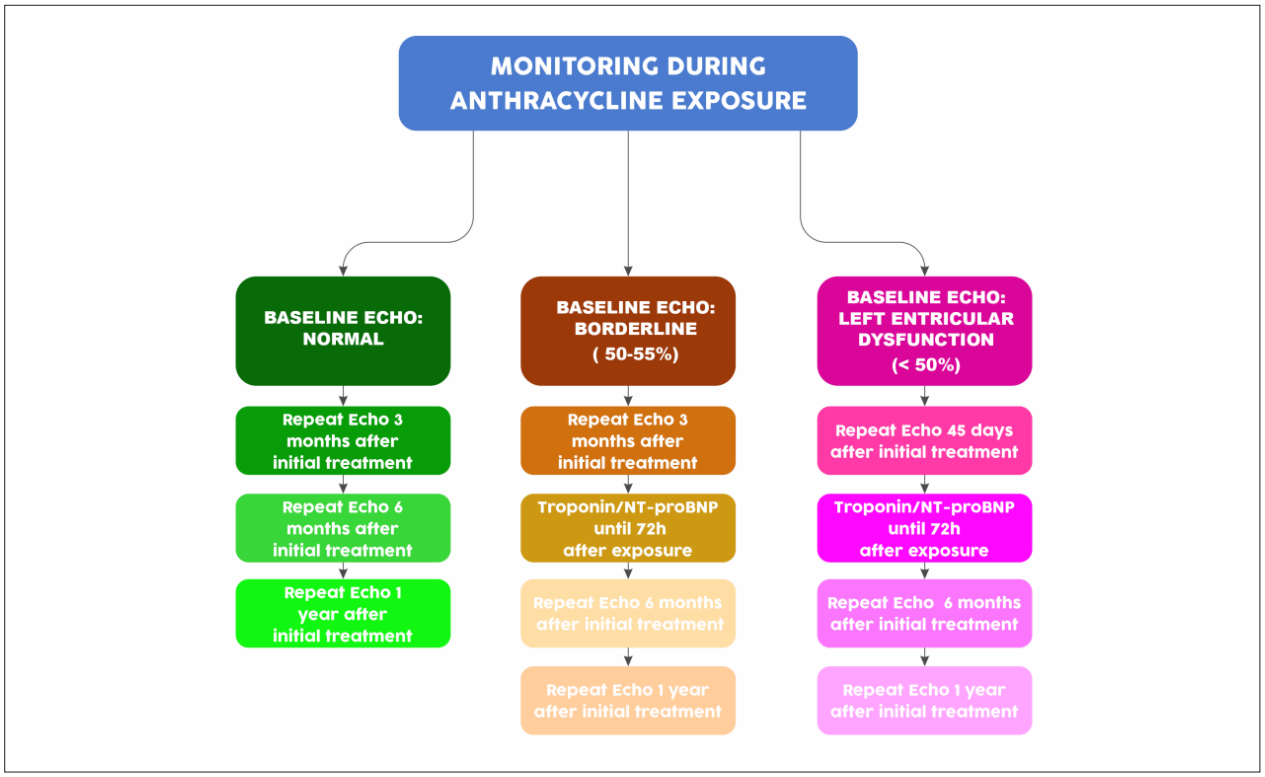


Figure 3 – *Echocardiographic monitoring and analysis of biomarkers in patients using anthracyclines suggested by the Brazilian Society of Cardiology.13 Echo: echocardiogram; NT-proBNP: N-terminal pro-B-type natriuretic peptide; QT: chemotherapy.*

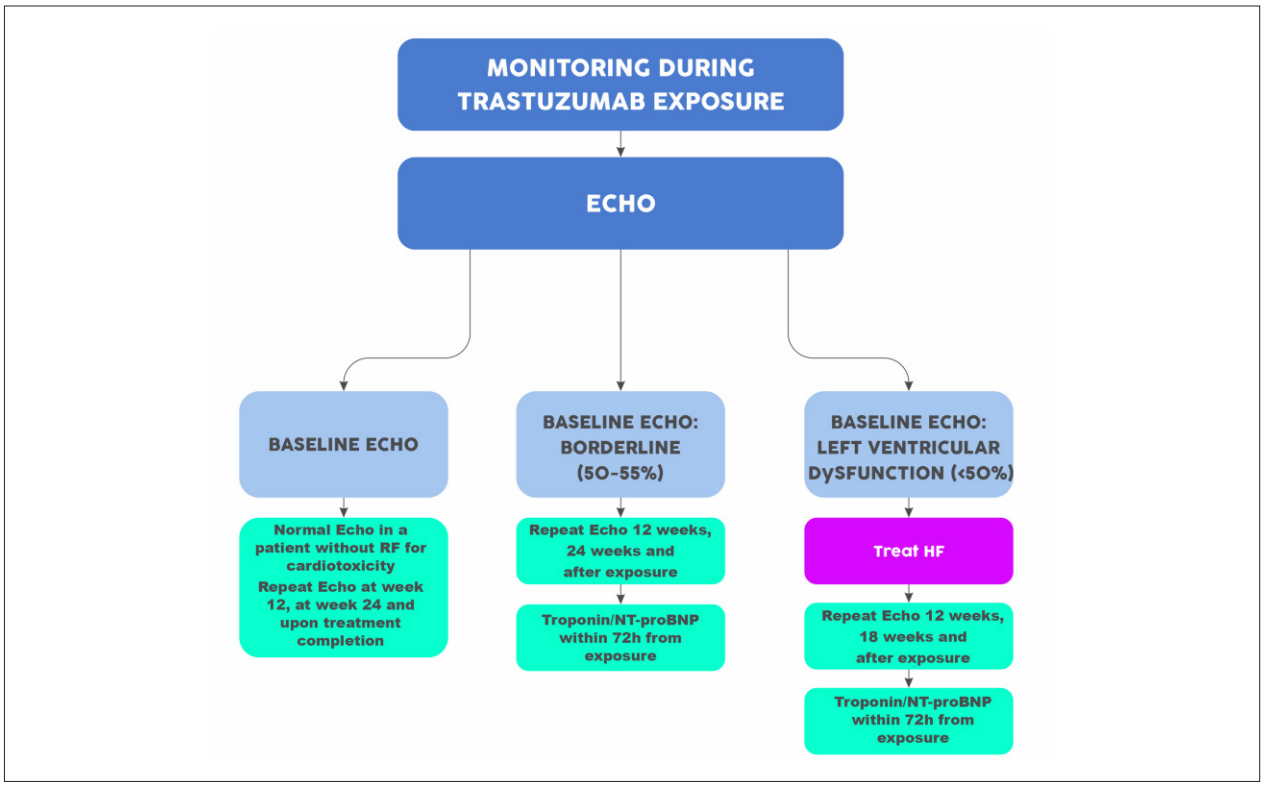


Figure 4 – *Echocardiographic monitoring and analysis of biomarkers in patients using anti-HER2 drugs suggested by the Brazilian Society of Cardiology.[13] Echo: echocardiogram; HF: heart failure; NT-proBNP: N-terminal pro-B-type natriuretic peptide; RF: risk factors.*

symptoms of heart failure or after 12% relative reduction in GLS. Comparing both groups, there was no difference in final ejection fraction. However, at the final follow-up, 44 patients in the GLS-guided arm were treated with cardioprotective drugs versus only 20 patients in the ejection fraction-guided arm. As a result, 21 patients (13.7%) in the ejection fraction-guided arm compared to 9 patients (5.8%) in the GLS-guided arm met criteria for cancer therapy-related cardiac dysfunction ($p = 0.022$), with a number needed to treat of 13. In a post-hoc analysis, the study also showed lower reduction in LVEF among GLS-guided patients (2.9%) compared to ejection fraction-guided patients (9.1%).

Primary prevention of chemotherapy-induced cardiomyopathy

Non-pharmacological prevention, such as stopping smoking, consuming healthy diet, and adopting moderate aerobic exercise, should always be stimulated to reduce cardiovascular risk.[26] It is also important to control weight, treat comorbidities, and, if possible, minimize cardiac radiation. Regarding pharmacological therapy, there are two approaches to primary prevention of ANT-induced cardiotoxicity: reducing the cardiotoxic effects of ANT and initiating a cardioprotective medication.

The first approach is made possible by decreasing cumulative dose of the agent (< 360 mg/m^2 of doxorubicin or equivalent dose of ANT analogues), using continuous infusion and giving preference to liposomal forms of the drug.[27] Preference should also be given to less cardiotoxic ANT analogues, such as epirubicin, idarubicin, and mitoxantrone.

In the second approach, cardioprotective medications are initiated with the aim of reducing myocardial injury. So far, only dexrazoxane has been approved by the United States Food and Drug Administration to avoid ANT cardiotoxicity in metastatic breast cancer patients who received > 300 mg/m^2 of doxorubicin.[28] Dexrazoxane is an iron chelator that changes topoisomerase 2β configuration, preventing ANT interaction and thus preventing its cardiotoxic effect. Different trials showed reduction of cardiovascular events and of the incidence of heart failure among breast cancer patients, and a systematic review and meta-analysis of randomized and nonrandomized trials on the efficacy of dexrazoxane in patients with breast cancer showed that dexrazoxane reduced the risk of clinical heart failure (risk ratio: 0.19; 95% confidence interval: 0.09 to 0.40; $p < 0.001$) and cardiac events (risk ratio: 0.36; 95% confidence interval: 0.27 to 0.49; $p < 0.001$) irrespective of previous ANT exposure. Furthermore, the rate of a partial or complete oncological response, overall survival, and progression-free survival were not affected by dexrazoxane.[29]

Cardiovascular drugs, such as beta-blockers, ACEI, and BRA, showed controversial results and are not recommended as a routine in patients under chemotherapy.[30] Earlier small randomized studies suggested that carvedilol[31] and nebivolol[32] were protective against LVEF changes. In one of the first randomized clinical trials comparing placebo versus carvedilol in patients treated with high doses of ANT chemotherapy, Kalay et al.[31] found a higher reduction in LVEF in the placebo group (69% to 53%) than in carvedilol (70% to 69%) ($p < 0.001$). Differently, the PRADA Trial (Prevention of Cardiac Dysfunction during Adjuvant Breast Cancer Therapy)[33] evaluated cardioprotection using metoprolol and candesartan in 130 patients and showed benefit of candesartan, with a less-pronounced decrease in LVEF compared to the metoprolol group and placebo. In 2021, the 2-year result of the PRADA trial[34] also showed that candesartan treatment was associated with a significant reduction in left ventricular end-diastolic volume compared with the non-candesartan group ($p = 0.021$) and attenuated decline in GLS ($p = 0.046$) at 2 years, but no difference was found in the metoprolol group, and there was no difference in cardiac troponins between groups.

Cardinale et al studied cardioprotection using enalapril, an ACEI widely used in the management of heart failure, in 114 patients who developed positive troponin during ANT treatment compared to placebo.[35] The enalapril group had significantly lower incidence of heart failure and asymptomatic ventricular dysfunction. The same author evaluated 273 patients that received enalapril as primary prevention compared to enalapril only in patients who developed positive troponin during chemotherapy.[36] There was no difference between groups, suggesting enalapril use could be triggered by troponin elevation.

The largest randomized trial evaluating carvedilol versus placebo in cardiotoxicity, the CECCY trial (Carvedilol Effect in Preventing Chemotherapy Induced Cardiotoxicity),[37] included 200 patients with breast cancer and use of ANT, and it showed no difference in LVEF between both groups. There was a slight decrease in left ventricle diastolic diameter in the carvedilol group. However, the rate of events was lower than calculated (14.5% in the carvedilol group and 13.5% in the placebo group), which may have interfered the results. Interestingly, in this study, patients in the carvedilol arm had lower troponin values than in the placebo arm, raising the possibility of subclinical cardiotoxicity protection. Table 2 shows the main trials evaluating cardioprotective medications in primary prevention.

When to start cardioprotective medications?

Current guidelines recommend assessment of cardiac toxicity using LVEF measurement. If, during treatment, a patient presents LVEF < 50%, cardioprotective medications should be started.[11,12] If LVEF drops below 40%, in addition to cardioprotective medications, antineoplastic treatment should be suspended temporarily based on discussion with the cardiologist and the oncologist (Figures 5 and 6). However, if the patient develops a GLS reduction (absolute ≥ 5% or relative ≥ 15%) or troponin elevation, there is, to date, no formal recommendation for suspension of chemotherapy agents, and cardioprotective medications may be considered.[12]

Conclusion

Regarding pharmacological cardioprotection, current evidence suggests that cardiovascular medications in all patients without stratification do not result in clinical benefit. However, an effort to identify subclinical myocardial damage should be made in order to recognize the subgroup that could benefit from intensive surveillance and cardioprotective medications. More sensitive and reproducible biomarkers such as troponin should be studied in association with GLS to precociously treat

Table 2 – Summary of the most important clinical trials in primary prevention of cardiotoxicity.

Study	Patients	Chemotherapy regimen	Cardioprotective drug	Primary outcome	Follow-up (months)
Cardinale[35] 2006	114	Epirubicin Idarubicin Daunorubicin	Enalapril	Cardiotoxicity incidence: Control: 43% Enalapril: 0% p < 0.001	12
Kalay[31] 2006	50	Doxorubicin Epirubicin	Carvedilol	LVEF change pre/post chemotherapy Placebo: 68.9%/52.3%; p < 0.001 Carvedilol: 70.5%/69.7%; p = 0.3	6
Georgakopoulos[38] 2010	125	Doxorubicin	Metoprolol Enalapril	No change in LVEF	12
Bosch[39] 2013	201	Idarubicin Daunorubicin	Carvedilol Enalapril	Mean change in LVEF reduction (%) Control: 3.1; p = 0.035 Enalapril + carvedilol: 0.17%; p = ns	6
Kaya[40] 2013	45	Doxorubicin Epirubicin	Nebivolol	LVEF change pre/post chemotherapy Placebo: 66.6%/57.5%; p = 0.001 Nebivolol: 65.6%/63.8%; p = 0.5	6
Gulati[33] 2016	126	Epirubicin	Metoprolol Candesartan	Mean change in LVEF reduction (%) Placebo: 2.6 Candesartan: 0.8; p = 0.026 Metoprolol: 1.6%; p = ns	6
Pituskin[41] 2017	94	Trastuzumab	Bisoprolol Perindopril	No change in LVEF	12
Avila[37] 2018	200	Doxorubicin	Carvedilol	No change in LVEF	6
Guglin[42] 2019	468	Trastuzumab	Lisinopril Carvedilol	Cardiotoxicity rate Placebo 47% versus lisinopril 37% versus carvedilol 31%	12

ACEI: angiotensin converting enzyme inhibitor; LVEF: left ventricular ejection fraction.

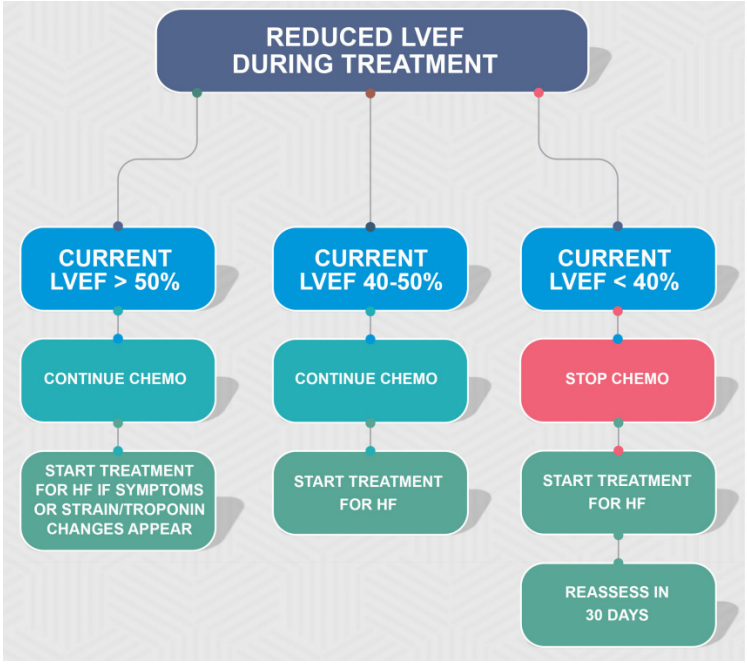


Figure 5 – *Flowchart of the Brazilian Society of Cardiology for the management of heart failure and ventricular dysfunction induced by anthracyclines. chemo: chemotherapy; HF: heart failure; LVEF: left ventricular ejection fraction.*

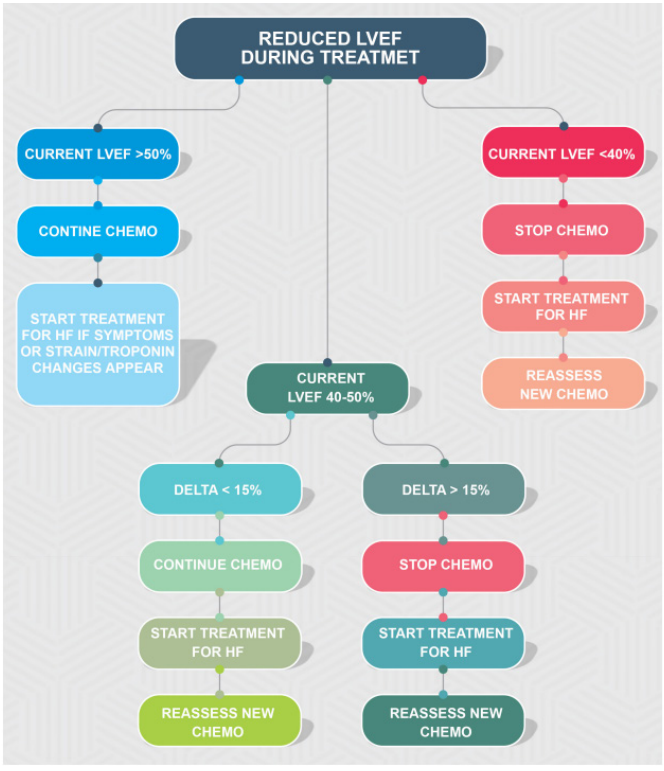


Figure 6 – *Flowchart of the Brazilian Society of Cardiology[13] for the management of heart failure and ventricular dysfunction induced by anti-HER2 therapy. chemo: chemotherapy; HF: heart failure; LVEF: left ventricular ejection fraction.*

cardiovascular dysfunction related to chemotherapy and reduce morbidity and mortality in this population.

Author Contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Writing of the manuscript, Critical revision of the manuscript for intellectual content: Avila MS, Belfort DSP, Wanderley Júnior MRB.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Miller KD, Siegel RL, Lin CC, Mariotto AB, Kramer JL, Rowland JH, et al. Cancer Treatment and Survivorship Statistics, 2016. CA Cancer J Clin. 2016;66(4):271-89. doi: 10.3322/caac.21349.
2. Bloom MW, Hamo CE, Cardinale D, Ky B, Nohria A, Baer L, et al. Cancer Therapy-Related Cardiac Dysfunction and Heart Failure: Part 1: Definitions, Pathophysiology, Risk Factors, and Imaging. Circ Heart Fail. 2016;9(1):e002661. doi: 10.1161/CIRCHEARTFAILURE.115.002661.
3. Patnaik JL, Byers T, DiGuiseppi C, Dabelea D, Denberg TD. Cardiovascular Disease Competes with Breast Cancer as the Leading Cause of Death for Older Females Diagnosed with Breast Cancer: A Retrospective Cohort Study. Breast Cancer Res. 2011;13(3):R64. doi: 10.1186/bcr2901.
4. Narezkina A, Nasim K. Anthracycline Cardiotoxicity. Circ Heart Fail. 2019;12(3):e005910. doi: 10.1161/CIRCHEARTFAILURE.119.005910.

5. Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, et al. Expert Consensus for Multimodality Imaging Evaluation of Adult Patients During and After Cancer Therapy: A Report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2014;27(9):911-39. doi: 10.1016/j.echo.2014.07.012.

6. Cardinale D, Colombo A, Lamantia G, Colombo N, Civelli M, De Giacomi G, et al. Anthracycline-induced Cardiomyopathy: Clinical Relevance and Response to Pharmacologic Therapy. J Am Coll Cardiol. 2010;55(3):213-20. doi: 10.1016/j.jacc.2009.03.095.

7. Cardinale D, Colombo A, Bacchiani G, Tedeschi I, Meroni CA, Veglia F, et al. Early Detection of Anthracycline Cardiotoxicity and Improvement with Heart Failure Therapy. Circulation. 2015;131(22):1981-8. doi: 10.1161/CIRCULATIONAHA.114.013777.

8. Nolan MT, Marwick TH, Plana JC, Li Z, Ness KK, Joshi VM, et al. Effect of Traditional Heart Failure Risk Factors on Myocardial Dysfunction in Adult Survivors of Childhood Cancer. JACC Cardiovasc Imaging. 2018;11(8):1202-03. doi: 10.1016/j.jcmg.2017.12.011.

9. Ezaz G, Long JB, Gross CP, Chen J. Risk Prediction Model for Heart Failure and Cardiomyopathy After Adjuvant Trastuzumab Therapy for Breast Cancer. J Am Heart Assoc. 2014;3(1):e000472. doi: 10.1161/JAHA.113.000472.

10. López-Fernández T, Thavendiranathan P. Emerging Cardiac Imaging Modalities for the Early Detection of Cardiotoxicity Due to Anticancer Therapies. Rev Esp Cardiol. 2017;70(6):487-495. doi: 10.1016/j.rec.2017.01.004.

11. Čelutkienė J, Pudil R, López-Fernández T, Grapsa J, Nihoyannopoulos P, Bergler-Klein J, et al. Role of Cardiovascular Imaging in Cancer Patients Receiving Cardiotoxic Therapies: A Position Statement on Behalf of the Heart Failure Association (HFA), the European Association of Cardiovascular Imaging (EACVI) and the Cardio-Oncology Council of the European Society of Cardiology (ESC). Eur J Heart Fail. 2020;22(9):1504-24. doi: 10.1002/ejhf.1957.

12. Dobson R, Ghosh AK, Ky B, Marwick T, Stout M, Harkness A, et al. BSE and BCOS Guideline for Transthoracic Echocardiographic Assessment of Adult Cancer Patients Receiving Anthracyclines and/or Trastuzumab. JACC CardioOncol. 2021;3(1):1-16. doi: 10.1016/j.jaccao.2021.01.011.

13. Hajjar LA, Costa IBSDSD, Lopes MACQ, Hoff PMG, Diz MDPE, Fonseca SMR, et al. Brazilian Cardio-oncology Guideline - 2020. Arq Bras Cardiol. 2020;115(5):1006-43. doi: 10.36660/abc.20201006.

14. Henri C, Heinonen T, Tardif JC. The Role of Biomarkers in Decreasing Risk of Cardiac Toxicity after Cancer Therapy. Biomark Cancer. 2016;8(Suppl 2):39-45. doi: 10.4137/BIC.S31798.

15. Oikonomou EK, Kokkinidis DG, Kampaktsis PN, Amir EA, Marwick TH, Gupta D, et al. Assessment of Prognostic Value of Left Ventricular Global Longitudinal Strain for Early Prediction of Chemotherapy-Induced Cardiotoxicity: A Systematic Review and Meta-analysis. JAMA Cardiol. 2019;4(10):1007-18. doi: 10.1001/jamacardio.2019.2952.

16. Katrukha IA, Katrukha AG. Myocardial Injury and the Release of Troponins I and T in the Blood of Patients. Clin Chem. 2021;67(1):124-30. doi: 10.1093/clinchem/hvaa281.

17. Cardinale D, Sandri MT, Colombo A, Colombo N, Boeri M, Lamantia G, et al. Prognostic Value of Troponin I in Cardiac Risk Stratification of Cancer Patients Undergoing High-Dose Chemotherapy. Circulation. 2004;109(22):2749-54. doi: 10.1161/01.CIR.0000130926.51766.CC.

18. Cardinale D, Sandri MT, Martinoni A, Tricca A, Civelli M, Lamantia G, et al. Left Ventricular Dysfunction Predicted by Early Troponin I Release After High-Dose Chemotherapy. J Am Coll Cardiol. 2000;36(2):517-22. doi: 10.1016/s0735-1097(00)00748-8.

19. Cardinale D, Sandri MT, Martinoni A, Borghini E, Civelli M, Lamantia G, et al. Myocardial Injury Revealed by Plasma Troponin I in Breast Cancer Treated with High-Dose Chemotherapy. Ann Oncol. 2002;13(5):710-5. doi: 10.1093/annonc/mdf170.

20. Hayakawa H, Komada Y, Hirayama M, Hori H, Ito M, Sakurai M. Plasma Levels of Natriuretic Peptides in Relation to Doxorubicin-Induced Cardiotoxicity and Cardiac Function in Children with Cancer. Med Pediatr Oncol. 2001;37(1):4-9. doi: 10.1002/mpo.1155.

21. Sherief LM, Kamal AG, Khalek EA, Kamal NM, Soliman AA, Esh AM. Biomarkers and Early Detection of Late Onset Anthracycline-Induced Cardiotoxicity in Children. Hematology. 2012;17(3):151-6. doi: 10.1179/102453312X13376952196412.

22. Mavinkurve-Groothuis AM, Marcus KA, Pourier M, Loonen J, Feuth T, Hoogerbrugge PM, et al. Myocardial 2D Strain Echocardiography and Cardiac Biomarkers in Children During and Shortly After Anthracycline Therapy for Acute lymphoblastic Leukaemia (ALL): A Prospective Study. Eur Heart J Cardiovasc Imaging. 2013;14(6):562-9. doi: 10.1093/ehjci/jes217.

23. Mornoş C, Petrescu L. Early Detection of Anthracycline-Mediated Cardiotoxicity: The Value of Considering Both Global Longitudinal Left Ventricular Strain and Twist. Can J Physiol Pharmacol. 2013;91(8):601-7. doi: 10.1139/cjpp-2012-0398.

24. Charbonnel C, Convers-Domart R, Rigaudeau S, Taksin AL, Baron N, Lambert J, et al. Assessment of Global Longitudinal Strain at Low-Dose Anthracycline-Based Chemotherapy, for the Prediction of Subsequent Cardiotoxicity. Eur Heart J Cardiovasc Imaging. 2017;18(4):392-401. doi: 10.1093/ehjci/jew223.

25. Thavendiranathan P, Negishi T, Somerset E, Negishi K, Penicka M, Lemieux J, et al. Strain-Guided Management of Potentially Cardiotoxic Cancer Therapy. J Am Coll Cardiol. 2021;77(4):392-401. doi: 10.1016/j.jacc.2020.11.020.

26. Avila MS, Siqueira SRR, Ferreira SMA, Bocchi EA. Prevention and Treatment of Chemotherapy-Induced Cardiotoxicity. Methodist Debakey Cardiovasc J. 2019;15(4):267-73. doi: 10.14797/mdcj-15-4-267.

27. van Dalen EC, Michiels EM, Caron HN, Kremer LC. Different Anthracycline Derivates for Reducing Cardiotoxicity in Cancer Patients. Cochrane Database Syst Rev. 2010;2010(5):CD005006. doi: 10.1002/14651858.CD005006.pub4.

28. Lyu YL, Kerrigan JE, Lin CP, Azarova AM, Tsai YC, Ban Y, et al. Topoisomerase IIbeta Mediated DNA Double-Strand Breaks: Implications in Doxorubicin Cardiotoxicity and Prevention by Dexrazoxane. Cancer Res. 2007;67(18):8839-46. doi: 10.1158/0008-5472.CAN-07-1649.

29. Macedo AVS, Hajjar LA, Lyon AR, Nascimento BR, Putzu A, Rossi L, et al. Efficacy of Dexrazoxane in Preventing Anthracycline Cardiotoxicity in Breast Cancer. JACC CardioOncol. 2019;1(1):68-79. doi: 10.1016/j.jaccao.2019.08.003.

30. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M, et al. 2016 ESC Position Paper on Cancer Treatments and Cardiovascular Toxicity Developed Under the Auspices of the ESC Committee for Practice Guidelines: The Task Force for Cancer Treatments and cardiovascular Toxicity of the European Society of Cardiology (ESC). Eur Heart J. 2016;37(36):2768-801. doi: 10.1093/eurheartj/ehw211.

31. Kalay N, Basar E, Ozdogru I, Er O, Cetinkaya Y, Dogan A, et al. Protective Effects of carvedilol Against Anthracycline-Induced Cardiomyopathy. J Am Coll Cardiol. 2006;48(11):2258-62. doi: 10.1016/j.jacc.2006.07.052.

32. Mohamed EA, Kassem HH. Protective Effect of Nebivolol on Doxorubicin-Induced Cardiotoxicity in Rats. Arch Med Sci. 2018;14(6):1450-58. doi: 10.5114/aoms.2018.79008.

33. Gulati G, Heck SL, Ree AH, Hoffmann P, Schulz-Menger J, Fagerland MW, et al. Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy (PRADA): a 2 × 2 Factorial, Randomized, Placebo-Controlled, Double-Blind Clinical Trial of Candesartan and Metoprolol. Eur Heart J. 2016;37(21):1671-80. doi: 10.1093/eurheartj/ehw022.

34. Heck SL, Mecinaj A, Ree AH, Hoffmann P, Schulz-Menger J, Fagerland MW, et al. Prevention of Cardiac Dysfunction During Adjuvant Breast

Cancer Therapy (PRADA): Extended Follow-Up of a 2×2 Factorial, Randomized, Placebo-Controlled, Double-Blind Clinical Trial of Candesartan and Metoprolol. Circulation. 2021;143(25):2431-40. doi: 10.1161/CIRCULATIONAHA.121.054698.

35. Cardinale D, Colombo A, Sandri MT, Lamantia G, Colombo N, Civelli M, et al. Prevention of High-Dose Chemotherapy-Induced Cardiotoxicity in High-Risk Patients by Angiotensin-Converting Enzyme Inhibition. Circulation. 2006;114(23):2474-81. doi: 10.1161/CIRCULATIONAHA.106.635144.

36. Cardinale D, Ciceri F, Latini R, Franzosi MG, Sandri MT, Civelli M, et al. Anthracycline-Induced Cardiotoxicity: A Multicenter Randomised Trial Comparing two Strategies for Guiding Prevention with Enalapril: The International CardioOncology Society-one trial. Eur J Cancer. 2018;94:126-37. doi: 10.1016/j.ejca.2018.02.005.

37. Avila MS, Ayub-Ferreira SM, Wanderley MRB Jr, Cruz FD, Brandão SMG, Rigaud VOC, et al. Carvedilol for Prevention of Chemotherapy-Related Cardiotoxicity: The CECCY Trial. J Am Coll Cardiol. 2018;71(20):2281-90. doi: 10.1016/j.jacc.2018.02.049.

38. Georgakopoulos P, Roussou P, Matsakas E, Karavidas A, Anagnostopoulos N, Marinakis T, et al. Cardioprotective Effect of Metoprolol and Enalapril in Doxorubicin-Treated Lymphoma Patients: A Prospective, Parallel-Group, Randomized, Controlled Study with 36-Month Follow-Up. Am J Hematol. 2010;85(11):894-6. doi: 10.1002/ajh.21840.

39. Bosch X, Rovira M, Sitges M, Domènech A, Ortiz-Pérez JT, Caralt TM, et al. Enalapril and Carvedilol for Preventing Chemotherapy-Induced Left Ventricular Systolic Dysfunction in Patients with Malignant Hemopathies: The OVERCOME trial (preventiOn of left Ventricular dysfunction with Enalapril and caRvedilol in patients submitted to intensive ChemOtherapy for the treatment of Malignant hEmopathies). J Am Coll Cardiol. 2013;61(23):2355-62. doi: 10.1016/j.jacc.2013.02.072.

40. Kaya MG, Ozkan M, Gunebakmaz O, Akkaya H, Kaya EG, Akpek M, et al. Protective Effects of Nebivolol Against Anthracycline-Induced Cardiomyopathy: A Randomized Control Study. Int J Cardiol. 2013;167(5):2306-10. doi: 10.1016/j.ijcard.2012.06.023.

41. Pituskin E, Mackey JR, Koshman S, Jassal D, Pitz M, Haykowsky MJ, et al. Multidisciplinary Approach to Novel Therapies in Cardio-Oncology Research (MANTICORE 101-Breast): A Randomized Trial for the Prevention of Trastuzumab-Associated Cardiotoxicity. J Clin Oncol. 2017;35(8):870-77. doi: 10.1200/JCO.2016.68.7830.

42. Guglin M, Krischer J, Tamura R, Fink A, Bello-Matricaria L, McCaskill-Stevens W, et al. Randomized Trial of Lisinopril Versus Carvedilol to Prevent Trastuzumab Cardiotoxicity in Patients With Breast Cancer. J Am Coll Cardiol. 2019;73(22):2859-2868. doi: 10.1016/j.jacc.2019.03.495.

Review Article

Pharmacological Treatment in Patients with Advanced Heart Failure: Recommendations and Challenges

Fernanda Scussel[1]

Santa Casa de Misericórdia de Curitiba,[1] *Curitiba, PR – Brazil*

Abstract

Heart failure is a highly prevalent condition, and a series of new therapies have emerged over the past years, improving patients' survival and quality of life, simultaneously making its management more complex. When treating patients with advanced heart failure, that is, with persistent limiting symptoms and recurrent hospitalizations, it is usually even more challenging to manage cases, given that, in addition to frequently having characteristics that would exclude them from most clinical studies, they pose a series of difficulties to optimizing therapies, mainly due to symptomatic hypotension and renal dysfunction, but also due to difficulty in adhering to the growing list of medications, high costs, and poor understanding of their own disease. The concept that is currently in vogue is that therapeutic optimization, including the 4 fundamental drugs for the treatment of heart failure with reduced ejection fraction (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers/angiotensin receptor-neprilysin inhibitors, beta-blockers, aldosterone receptor antagonists, and sodium-glucose cotransporter-2 inhibitors), should be carried out quickly, within 4 weeks after diagnosis or hospitalization for decompensation, in the event that the patient is not already using the 4 classes. This may be a somewhat "daring" goal when treating patients in more advanced stages. In these cases, some strategies can help to achieve the best tolerated treatment possible, with good control of symptoms and improved survival. Furthermore, intolerance to clinical treatment is also a marker of advanced disease in itself and should be considered a reason for referral to centers specializing in advanced heart failure whenever possible.

Introduction

Heart failure (HF) is a highly prevalent condition, for which a series of pharmacological treatments and devices have been developed, with significant improvement in patient survival and quality of life. In spite of this, a portion of patients follow the natural course of the disease, reaching more advanced stages, defined as stage D.[1] Even patients who initially benefit from available therapies may eventually progress to the advanced form.

Definitions of HF differ according to the source analyzed, but they all agree on the point of persistent severe symptoms (New York Heart Association functional class [NYHA FC] III to IV) and repeated hospitalizations, in spite of optimized maximum tolerated therapy.[2-5] It is necessary to keep in mind that the concept of advanced HF goes beyond the presence of left ventricular dysfunction, given that patients with preserved ejection fraction (EF) can also be characterized as such, as well as those with congenital heart disease, severe valve disease without the possibility of intervention, and isolated right ventricular dysfunction.[3] That notwithstanding, the therapeutic options discussed in the following text are applied to patients with reduced EF. Another point of convergence in the majority of documents that deal with advanced HF is the issue of intolerance to maximal therapeutic optimization, generally due to symptomatic hypotension and renal dysfunction, with or without hyperkalemia. Moreover, as suggested by the guidelines,[3,6-8] other issues that are frequently present in this group of patients also render clinical optimization difficult, such as advanced age, associated comorbidities, and polypharmacy, with consequent difficulty in adherence, in addition to increasing costs.

The objective of this review is to bring together data from evidence on pharmacological treatment in this specific group of patients, as well as challenges in daily clinical practice.

Classical pharmacological treatment

In general, patients with more advanced disease characteristics end up being underrepresented in most clinical studies. In the PARADIGM-HF study, which randomized more than 8000 patients with EF < 40% (subsequently changed to ≤ 35%) to receive either sacubitril/valsartan (S/V) or enalapril, showing an important reduction in all-cause mortality, deaths due to cardiovascular causes, and hospitalization for HF, in addition to a reduction in sudden death, < 1% of patients were categorized as NYHA FC IV.[9] Approximately 20% of patients screened during the run-in period (4 to 6 weeks, to test drug tolerance) could not be included due to intolerance to the target drug dose, hypotension, or worsening renal function. In the PIONEER study, which evaluated the use of S/V in patients with decompensated HF, only 9% were in NYHA FC IV.[10]

The LIFE study was developed in an attempt to fill this gap in relation to the use of S/V in patients with advanced HF (defined as EF ≤ 35%, NYHA FC IV, BNP ≥ 250 pg/mL or NT-proBNP ≥ 800 pg/mL, and ≥ 1 objective finding of advanced disease).[11] Patients were randomized to receive S/V or valsartan alone after a 7-day run-in period to evaluate

Keywords

Heart Failure; Drug Therapy.

Mailing Address: Fernanda Scussel •
Rua Nunes Machado, 471, apto 1402. Postal Code 80250-000, Curitiba, PR - Brazil
E-mail: ferscussel@gmail.com
Manuscript received January 29, 2022, revised manuscript February 01, 2022, accepted February 25, 2022

DOI: https://doi.org/10.36660/abchf.20220021

tolerance to the initial S/V dose of 24/26 mg twice daily. The primary endpoint included proportional change in NT-proBNP at 24 weeks, evaluated by the area under the curve. Secondary outcomes included cardiovascular mortality, hospitalization for HF, hypotension, and other markers of drug tolerance. It was necessary to interrupt the study early due to the COVID-19 pandemic, and the analysis of the results was performed with the 335 patients included up to the moment the study was interrupted; the initial objective had been 400 patients. There were no differences between the groups in any of the outcomes evaluated, and the achieved medication dose was < 50% of the target dose for both groups. In spite of the study limitations, it is starting to become clear that patients in this group do in fact have their own peculiarities in terms of management, and they should not be treated in the same way as patients in earlier stages. Intolerance to clinical treatment should be considered a reason for referral to centers specializing in advanced HF to evaluate indication of other (non-pharmacological) therapies.

Among the studies evaluating the effects of sodium-glucose cotransporter-2 (SGLT2) inhibitors in patients with HF and reduced EF, with or without type 2 diabetes, < 1% of patients in the DAPA-HF study[12] were in NYHA FC IV. Compared to this, patients included in the EMPEROR-REDUCED study[13] had lower EF, higher levels of NT-proBNP, and lower glomerular filtration rate (GFR), reflecting a population with greater severity. A meta-analysis that included both studies showed a 13% reduction in all-cause mortality, a 14% reduction in cardiovascular mortality, and an important reduction in hospitalizations for HF, which had already been demonstrated by both studies individually. However, in subgroup analysis, the effect was shown to be attenuated, although still significant, in patients in NYHA FC III to IV.[14] Because these medications have modest effects on blood pressure, in addition to an excellent safety profile, they tend to be well tolerated, even by the most borderline patients, and their initiation in conjunction with beta-blockers has been proposed as a first step in treatment-naive patients or patients whose treatment has been suspended due to more severe decompensation, because, thanks to their natriuretic effect, they can help to counterbalance the symptoms of clinical worsening that may arise at the beginning of beta-blocker therapy.[15]

In relation to older treatments for HF, there are some studies available that have included outpatients in more advanced stages,[16-20] demonstrating consistently beneficial results. The COPERNICUS study[17] was the largest study that evaluated patients with NYHA FC III to IV and EF < 25%, with a significant reduction in deaths and hospitalizations due to HF, in addition to good patient tolerance to the drug. Meta-analysis of randomized trials evaluating the effect of beta-blockers in patients in NYHA FC IV reiterated this concept.[21]

In spite of this, concerns still exist in relation to beta-blocker use, especially at the recommended doses, in patients with more advanced disease. A non-randomized study that evaluated the use of carvedilol in patients in NYHA FC IV showed that, although patients were more likely to experience worsening HF soon after starting the medication, the majority were able to continue with the therapy after an initial period of adjustments, and they showed a greater magnitude of symptomatic improvement after 3 months of treatment.[22,23] Hypotension and hyponatremia, which are conditions that reflect more severe and possibly more congested patients, are predictors of worsening HF after starting carvedilol.[22,23] Patients in more advanced stages require closer follow-up when starting beta-blockers, often requiring a temporary increase in diuretic dose, but these patients tolerate the therapy well and they benefit even more from it. Prior to initiation or progression of the beta-blocker dose, patients must be minimally compensated in order to tolerate the elevated filling pressures and reduced cardiac output, which are mild, yet relevant in these cases.

Aldosterone receptor antagonists are one of the most underused classes in patients with HF and reduced EF,[24-27] although they have shown 15% to 30% reduction in mortality and up to 40% reduction in rehospitalization in the main studies.[19,28,29] The main precautions are related to worsening renal function, hyperkalemia, and eventually hypotension. Regarding this last issue, an interesting study retrospectively analyzed patients included in the RALES and EPHESUS studies (4396 patients in total), subdivided according to baseline systolic blood pressure (≤ 105, > 105 and ≤ 115, > 115 and ≤ 125, > 125 and ≤ 135, and > 135 mmHg) showing no significant reduction in blood pressure between the drug and placebo, in contrast to what occurs in the treatment of hypertensive patients.[30] Furthermore, the benefit of relative reduction in mortality was consistent across all subgroups analyzed. Taking into account that patients with systolic blood pressure ≤ 105 mmHg were more severe patients due to several characteristics analyzed, these patients benefit even more from the proposed treatment. The concern regarding a possible worsening of renal function and hyperkalemia is justified; however, we currently have some strategies to minimize these effects, which will be described subsequently.

In patients with refractory symptoms, the use of digoxin can also be considered, especially as an adjunct to heart rate control in cases of atrial fibrillation, paying attention to the risk of toxicity, especially in women, patients with low weight, and patients with renal dysfunction.[31,32] The therapy should ideally be adjusted according to drug serum level. Data from more contemporary cohorts of patients with HF are conflicting in relation to the benefits and safety of using digoxin, especially when in sinus rhythm.[31,33] Discontinuation of digoxin in patients hospitalized for HF seems to be associated with higher rates of rehospitalization, even when they are receiving optimized treatment with other therapies.[34]

The study that evaluated the effects of ivabradine in patients with HF and reduced EF did not include patients on NYHA FC IV.[35] However, the drug seems interesting for the profile of more advanced patients in certain contexts, as it reduces heart rate, without a negative inotropic effect.[36] A subanalysis of the SHIFT study using echocardiography assessment showed an increase in systolic volume, by improving ventricular-arterial coupling with a reduction in heart rate.[37] It has been postulated that ivabradine may be useful in patients with sinus tachycardia induced by the use of inotropes, especially dobutamine.[38] Sinus tachycardia is usually a compensatory mechanism, which attempts to maintain minimally adequate cardiac output. However, the direct physiological relationship

between increased heart rate and increased myocardial contractility observed in normal hearts is lost when there is myocardial dysfunction, a condition in which there is a paradoxical reduction in contractile force with higher frequencies.[39] Accordingly, ivabradine could contribute to mitigating excessive tachycardia in patients using an inotrope, controlling heart rate without causing negative inotropism and potentially improving hemodynamics. This hypothesis has only been tested in animal studies and small studies in patients with HF, evaluating short-term hemodynamic effects, and the data cannot be extrapolated to clinical practice.[40,41] Formally, the indication for the use of ivabradine in patients with advanced HF is the same as that applied to other profiles of patients with HF and reduced EF.

Given the various therapeutic options with proven positive impact on HF with reduced EF, taking into account that the benefit of each drug is independent of the presence of the others and that the mechanisms of action are complementary, individualization appears to be the best strategy.[42] Patients present with different phenotypes, which reflect different needs, and it seems to be a suitable method define the pharmacological strategy in a more personalized manner, maintaining the objective of including all of the fundamental classes (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers/angiotensin receptor-neprilysin inhibitors [ACEI/ARB/ARNI], beta-blockers, aldosterone antagonists, and SGLT2 inhibitors).

New pharmacological treatments

Omecamtiv mecarbil is a more recent medication that has been tested in HF. It acts as a specific ligand of cardiac myosin, optimizing the actin-myosin interaction in the heart muscle, promoting improved contractility (known as the "myotropic" effect). Unlike other medications that increase myocardial contractility, omecantiv does not increase the influx of calcium into the myocyte, considerably reducing the risk of arrhythmias and myocardial ischemia. Initial pharmacokinetic studies showed an increase in ventricular ejection time and systolic volume, in addition to a reduction in left ventricular end-systolic and diastolic volumes.[43]

The first study to evaluate clinical outcomes of omecantiv mecarbil in HF was the GALACTIC-HF, which randomized more than 8000 patients between 18 and 85 years of age, NYHA FC II to IV (although there were only 124 NYHA FC IV patients in each group), with EF < 35%, who were hospitalized or had been hospitalized during the last year, to receive placebo or omecantiv, with dose guided by serum level measurement. Patients using inotropes, patients with systolic blood pressure < 85 mmHg, and patients with GFR < 20 mL/min/1.73 m^2 were excluded. The primary endpoint included time to first HF-related event (hospitalization, urgent emergency room, or outpatient visit) or death due to cardiovascular causes. There was an 8% reduction in the primary outcome (hazard ratio 0.92, 95% confidence interval 0.86 to 0.99; p = 0.03), with no reduction in cardiovascular mortality. There was no difference in the number of adverse events between the groups. Hypotension, worsening of renal function, and hyperkalemia also did not occur.[44]

Subgroup analysis was performed according to EF (divided into quartiles: EF ≤ 22%, EF 23% to 28%, EF 29% to 32%, and EF ≥ 33%); this analysis had already been pre-specified in the initial study design. The primary endpoint event rate was significantly higher (up to 80% higher) in the quartile with the lowest EF compared to the one with the highest EF, and the benefit of therapy was significantly greater in patients with EF ≤ 28% (hazard ratio 0.84; 95% confidence interval: 0.77 to 0.92; p = 0.0003), when compared to patients with EF > 28% (hazard ratio 1.04; 95% confidence interval: 0.94 to 1.16; p = 0.45). This difference was due to the reduction in hospitalizations rather than cardiovascular mortality.[45] In spite of the observed drop in natriuretic peptide levels, there was no symptomatic improvement (evaluated by the Kansas City Cardiomyopathy Questionnaire).

With these data, it is possible to speculate regarding the potential use of this medication in patients with advanced HF, considering the pathophysiological rationale behind its functioning, the evidence of greater benefit in subgroups with greater ventricular dysfunction, and the absence of side effects that are common in this group of patients, such as hypotension and renal dysfunction, but more studies will be needed to confirm these conclusions.

Vericiguat is a molecule that acts by stimulating soluble cyclic guanosine monophosphate through a mechanism that is independent of nitric oxide, but it also increases the sensitivity of cyclic guanosine monophosphate to endogenous nitric oxide, stabilizing the binding of nitric oxide with its receptor, finally improving myocardial function and exerting a vasodilating effect. The medication was approved by the United States Food and Drug Administration in January 2021, following the favorable results of the VICTORIA study,[46] which randomized patients with EF < 45%, NYHA FC II to IV, and elevated natriuretic peptides (NT-proBNP > 1000 pg/mL or > 1600 pg/mL with atrial fibrillation), with recent worsening (hospitalization during the past 6 months or use of parenteral diuretic therapy on an outpatient basis) to receive placebo or vericiguat, at a target dose of 10 mg/day. Patients with systolic blood pressure < 100 mmHg and patients who were receiving inotropes were excluded. It is interesting to note that patient recruitment occurred more rapidly than expected, and the number of primary outcome events was also higher than initially calculated, thus representing a more severe population. There was a significant reduction in the outcome of rehospitalization for HF at a mean follow-up of 10 months. Symptomatic hypotension was more frequent in patients using the drug, but there was no significant difference with the placebo group. Anemia was a more common adverse event in patients receiving vericiguat, and the mechanism of this change is not well understood. Subgroup analysis according to NT-proBNP levels (divided into quartiles) showed no benefit in the quartile with higher dosages (> 5314 pg/mL), possibly reflecting a population with very advanced disease, with indication for other non-pharmacological therapies, or even palliative care. Vericiguat became a class IIb recommendation in the 2021 European HF Guideline, for patients with HF with reduced EF, NYHA FC II to IV, and worsening HF in spite of treatment with beta-blockers, ACEI/ARB or ARNI, and aldosterone antagonists.[7]

Renal dysfunction and hyperkalemia in patients with advanced HF

The presence of renal dysfunction in patients with HF is a marker of higher morbidity and mortality, as well as advanced disease, when considering that the loss of renal function is secondary to the hemodynamic changes imposed by HF. In spite of this, these patients are known to receive the therapies classically indicated for this condition,[47,48] mainly renin-angiotensin-aldosterone system antagonists, less frequently.[49] Moreover, patients with chronic kidney disease are at an increased risk of developing HF, regardless of the presence of coronary artery disease.[50] In relation to patients with more advanced chronic kidney disease (grades 3 or 4), they are also extremely underrepresented in clinical studies. Data on the benefits and safety of the use of ACEI/ARB in these cases come mostly from observational studies. In general, the use of ACEI/ARB can worsen renal function, especially in the short term, and this implies worse prognosis; however, the benefit of therapy with ACEI/ARB is maintained, and it may even be greater.[51] In patients who initially present with chronic kidney disease (GFR ≤ 30 mL/min/m^2 or creatinine > 2.5 mg/dL), the benefit of using this class of drugs, when tolerated, is maintained.[52] Thus, the presence of renal dysfunction should not exclude the patient from trying to use ACEI/ARB and, more recently, ARNI, given that these patients, who are a at higher risk of events, tend to benefit more from treatments, even if at low doses, below those defined as target doses by classical studies, provided that they are followed more closely, with more frequent clinical and laboratory reassessments.

With respect to more recent therapies, subsequent analysis of the PARADIGM study showed that the reduction in GFR was smaller in the S/V group compared to patients who received enalapril, regardless of baseline renal function, in spite of an increase in urine albumin-creatinine ratio caused by S/V.[53] This increase was shown to be mild, and it stabilized after a few weeks of treatment. It is worth noting that the study excluded patients with GFR < 30 mL/min/1.73 m^2.

SGLT2 inhibitors have also been shown to be very favorable in this scenario, with results of less progression of renal dysfunction in long-term use,[54,55] in addition to a lower risk of hyperkalemia when used in conjunction with aldosterone antagonists.[56]

In relation to aldosterone receptor antagonists, recommendations tend to be more conservative when there is renal dysfunction, and their use is contraindicated when creatinine is > 2 mg/dL in women or > 2.5 mg/dL in men, due to the greater risk of worsening of renal function and hyperkalemia, without a clear accompanying benefit.[57] Once a patient already using an aldosterone antagonist develops more important renal dysfunction (GFR ≤ 30 mL/min/1.73 m^2), the medication should not routinely be discontinued, and each case may be individualized.[58]

Hyperkalemia is another frequent challenge during management of patients with HF, especially in those with some degree of impaired renal function, and it is associated with worse outcomes, mainly due to the lower use of therapies that block the renin-angiotensin-aldosterone system.[59-61] When there is mild hyperkalemia, routine non-suspension of these therapies was proposed by Ferreira JP et al.[62] in a recent review, where an algorithm for managing these patients was proposed to minimize the underutilization of therapies that have been proven to improve prognosis. The risk of hyperkalemia associated with the concomitant use of aldosterone antagonists is lower when using S/V when compared to enalapril,[63] which is one of the strategies proposed if the patient is not already using ARNI. The risk of hyperkalemia is also lower when an SGLT2 inhibitor is associated with treatment.[56]

The use of potassium chelators is another possibility. The use of patiromer (potassium ligand) has been tested in patients with HF, showing to be effective for this purpose,[64] and it is approved for management of hyperkalemia secondary to the use of renin-angiotensin-aldosterone system blockers in the United States and Europe, but it is still unavailable in Brazil. There are no data on efficacy and safety for calcium polystyrene sulfonate in this context. Studies are underway with the objective of evaluating whether the use of chelators, with a consequent increase in the use of renin-angiotensin-aldosterone system blockers, improves outcomes in patients with HF.

Hypotension and difficulty in dose progression

Optimizing therapy and managing symptoms in patients with more advanced disease can be quite challenging. One of the most limiting issues in this regard is symptomatic hypotension. When this occurs, it is important to assess the possibility of hypovolemia, with the eventual need to reduce diuretic use[65] and carefully review all medications in use to check if there are any that are not related to the treatment of HF that may be contributing to hypotension, such as calcium channel blockers and medications for benign prostatic hyperplasia, among others. Fractioning the administration of medications throughout the day, avoiding simultaneous intake of ACEI/ARB/ARNI and beta-blockers can also be useful. It is possible to prioritize beta-blockers without alpha-adrenergic effect (metoprolol and bisoprolol), which therefore have less potential to cause hypotension.

Intolerance to ACEI/ARB use due to circulatory limitation (symptomatic hypotension) or renal limitation (significant worsening of renal function) is an important marker of severity and high risk of death, as well as need for mechanical circulatory support or heart transplantation within 6 months.[66] In this manner, these patients should ideally be referred for specialized evaluation.

Initiation of beta-blocker therapy in more advanced patients, although safe, when the disease is minimally compensated, can be more difficult for the patient to tolerate, as patients often experience a feeling of "clinical worsening," with fatigue, tiredness and drowsiness. In these cases, it is worthwhile to warn patients about this possible feeling of worsening and inform them that, with persistent use, it tends to improve. While more stable patients may have their medication titrated every 7 days, in patients with advanced HF, a longer interval between beta-blocker dose increments may be prudent.[67]

Beta-blocker intolerance is not a class effect; therefore, it is valid to try more than one option before defining a patient as intolerant to the drug.[68]

The benefits of fundamental pharmacological therapies (ACEI/ARB/ARNI, beta-blockers, and aldosterone antagonists) are evident and significant, even at low doses, and they are seen in the short term, on average in 30 days.[69-73] Thus, the association of therapies, even at doses below those considered as target doses, is a superior strategy for reducing outcomes in patients with HF,[74] and it often ends up being used in patients with more severe disease. The concept that using a low dose is better than not using the drug should always be taken into account when dealing with a more severe patient who does not tolerate progression.[75]

Reconsidering therapeutic goals in advanced HF

Keeping in mind the scarcity of quality data related to the real benefit of classically recommended therapies for HF with reduced EF in the subgroup of patients with advanced disease, much of daily practice ends up being based on the personal experience of professionals who routinely treat these patients.

As a rule, the treatments instituted aim to reduce disease progression and increase survival, but, when treating patients in more advanced stages, improvement of symptoms and quality of life should become one of the goals to be pursued, given that the vast majority will end up not being eligible or will not have access to advanced therapies, such as heart transplantation or circulatory assist devices.

In most cases, the hemodynamic alteration that generates limiting symptoms is the increase in resting filling pressures, caused by hypervolemia. When there is systemic congestion, gastrointestinal symptoms, such as loss of appetite, abdominal discomfort, and early satiety may predominate. A good part of referred patients with refractory symptoms can improve with adequate volume adjustment, which can be difficult to assess, especially in chronic patients.[76] In some cases, in addition to dose optimization and eventual association of diuretics, the use of nitrates can be both beneficial and symptomatic.[77]

Refractory congestion, with resistance to diuretics, is a scenario commonly found in patients with advanced disease, and it requires a targeted and specific approach for this purpose, which is not within the scope of this review.

Finally, it is important to discuss expectations regarding treatment with patients who have advanced HF. In some cases, symptom control becomes a priority, to the detriment of prolonging survival, and pharmacological treatment should be guided by prioritizing this objective.

Conclusion

Patients with advanced HF present several particularities in pharmacological management and optimization, with increasing complexity. This group of patients is expected to grow progressively, with increased survival promoted by the therapies that are currently available. Therefore, it is essential for there to be more studies focused on this profile of patients, as well as greater representation in clinical trials. Given that it is a marker of worse prognosis, difficulty in pharmacological management should be considered a reason for referral to specialized centers.

Author Contributions

Writing of the manuscript: Scussel F

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Card Fail. 2017;23(8):628-51. doi: 10.1016/j.cardfail.2017.04.014.
2. Crespo-Leiro MG, Metra M, Lund LH, Milicic D, Costanzo MR, Filippatos G, et al. Advanced heart Failure: A Position Statement of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2018;20(11):1505-35. doi: 10.1002/ejhf.1236.
3. Marcondes-Braga FG, Moura LAZ, Issa VS, Vieira JL, Rohde LE, Simões MV, et al. Emerging Topics Update of the Brazilian Heart Failure Guideline - 2021. Arq Bras Cardiol. 2021;116(6):1174-212. doi: 10.36660/abc.20210367.
4. Truby LK, Rogers JG. Advanced Heart Failure: Epidemiology, Diagnosis, and Therapeutic Approaches. JACC Heart Fail. 2020;8(7):523-36. doi: 10.1016/j.jchf.2020.01.014.
5. Fang JC, Ewald GA, Allen LA, Butler J, Westlake Canary CA, Colvin-Adams M, et al. Advanced (stage D) Heart Failure: A Statement from the Heart Failure Society of America Guidelines Committee. J Card Fail. 2015;21(6):519-34. doi: 10.1016/j.cardfail.2015.04.013.
6. Maddox TM, Januzzi JL Jr, Allen LA, Breathett K, Butler J, Davis LL, et al. 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2021;77(6):772-810. doi: 10.1016/j.jacc.2020.11.022.

7. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. Eur Heart J. 2021;42(36):3599-3726. doi: 10.1093/eurheartj/ehab368.

8. Rohde LEP, Montera MW, Bocchi EA, Clausell NO, Albuquerque DC, Rassi S, et al. Diretriz Brasileira de Insuficiência Cardíaca Crônica e Aguda. Arq Bras Cardiol. 2018;111(3):436-539.doi: 10.5935/abc.20180190.

9. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin Inhibition versus Enalapril in Heart Failure. N Engl J Med. 2014;371(11):993-1004. doi: 10.1056/NEJMoa1409077.

10. Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, et al. Angiotensin-Neprilysin Inhibition in Acute Decompensated Heart Failure. N Engl J Med. 2019;380(6):539-48. doi: 10.1056/NEJMoa1812851.

11. Mann DL, Greene SJ, Givertz MM, Vader JM, Starling RC, Ambrosy AP, et al. Sacubitril/Valsartan in Advanced Heart Failure With Reduced Ejection Fraction: Rationale and Design of the LIFE Trial. JACC Heart Fail. 2020;8(10):789-99. doi: 10.1016/j.jchf.2020.05.005.

12. McMurray JJV, DeMets DL, Inzucchi SE, Køber L, Kosiborod MN, Langkilde AM, et al. A Trial to Evaluate the Effect of the sodium-Glucose Co-Transporter 2 Inhibitor Dapagliflozin on Morbidity and Mortality in Patients with Heart Failure and Reduced Left Ventricular Ejection Fraction (DAPA-HF). Eur J Heart Fail. 2019;21(5):665-75. doi: 10.1002/ejhf.1432.

13. Packer M, Anker SD, Butler J, Filippatos G, Ferreira JP, Pocock SJ, et al. Effect of Empagliflozin on the Clinical Stability of Patients with Heart Failure and a Reduced Ejection Fraction: The EMPEROR-Reduced Trial. Circulation. 2021;143(4):326-36. doi: 10.1161/CIRCULATIONAHA.120.051783.

14. Zannad F, Ferreira JP, Pocock SJ, Anker SD, Butler J, Filippatos G, et al. SGLT2 Inhibitors in Patients with Heart Failure with Reduced Ejection Fraction: A Meta-Analysis of the EMPEROR-Reduced and DAPA-HF trials. Lancet. 2020;396(10254):819-29. doi: 10.1016/S0140-6736(20)31824-9.

15. McMurray JJV, Packer M. How Should we Sequence the Treatments for Heart Failure and a Reduced Ejection Fraction?: A Redefinition of Evidence-Based Medicine. Circulation. 2021;143(9):875-77. doi: 10.1161/CIRCULATIONAHA.120.052926.

16. CONSENSUS Trial Study Group. Effects of Enalapril on Mortality in Severe Congestive heart Failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med. 1987;316(23):1429-35. doi: 10.1056/NEJM198706043162301.

17. Packer M, Fowler MB, Roecker EB, Coats AJ, Katus HA, Krum H, et al. Effect of Carvedilol on the Morbidity of Patients with Severe Chronic Heart Failure: Results of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study. Circulation. 2002;106(17):2194-9. doi: 10.1161/01.cir.0000035653.72855.bf.

18. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, et al. The Effect of Carvedilol on Morbidity and Mortality in Patients with Chronic Heart Failure. U.S. Carvedilol Heart Failure Study Group. N Engl J Med. 1996;334(21):1349-55. doi: 10.1056/NEJM199605233342101.

19. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999;341(10):709-17. doi: 10.1056/NEJM199909023411001.

20. Cohn JN, Tam SW, Anand IS, Taylor AL, Sabolinski ML, Worcel M, et al. Isosorbide Dinitrate and Hydralazine in a Fixed-Dose Combination Produces Further Regression of Left Ventricular Remodeling in a Well-Treated Black Population with Heart Failure: Results from A-HeFT. J Card Fail. 2007;13(5):331-9. doi: 10.1016/j.cardfail.2007.03.001

21. Whorlow SL, Krum H. Meta-Analysis of Effect of Beta-Blocker Therapy on Mortality in Patients with New York Heart Association Class IV Chronic Congestive Heart Failure. Am J Cardiol. 2000;86(8):886-9. doi: 10.1016/s0002-9149(00)01114-0.

22. Macdonald PS, Keogh AM, Aboyoun CL, Lund M, Amor R, McCaffrey DJ. Tolerability and Efficacy of Carvedilol in Patients with New York Heart Association Class IV Heart Failure. J Am Coll Cardiol. 1999;33(4):924-31. doi: 10.1016/s0735-1097(98)00680-9.

23. Krum H, Sackner-Bernstein JD, Goldsmith RL, Kukin ML, Schwartz B, Penn J, et al. Double-Blind, Placebo-Controlled Study of the Long-Term Efficacy of Carvedilol in Patients with Severe Chronic Heart Failure. Circulation. 1995;92(6):1499-506. doi: 10.1161/01.cir.92.6.1499.

24. Albert NM, Yancy CW, Liang L, Zhao X, Hernandez AF, Peterson ED, et al. Use of Aldosterone Antagonists in Heart Failure. JAMA. 2009;302(15):1658-65. doi: 10.1001/jama.2009.1493.

25. Lachaine J, Beauchemin C, Ramos E. Use, Tolerability and Compliance of Spironolactone in the Treatment of Heart Failure. BMC Clin Pharmacol. 2011;11:4. doi: 10.1186/1472-6904-11-4.

26. Margolis J, Gerber RA, Roberts C, Gheorghiade M. Adherence to Aldosterone-Blocking Agents in Patients with Heart Failure. Am J Ther. 2010;17(5):446-54. doi: 10.1097/MJT.0b013e3181ea3213.

27. Samuel JL, Delcayre C. Heart failure: Aldosterone Antagonists are Underused by Clinicians. Nat Rev Cardiol. 2010;7(3):125-7. doi: 10.1038/nrcardio.2009.244.

28. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, et al. Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms. N Engl J Med. 2011;364(1):11-21. doi: 10.1056/NEJMoa1009492.

29. Pitt B, Williams G, Remme W, Martinez F, Lopez-Sendon J, Zannad F, et al. The EPHESUS Trial: Eplerenone in Patients with Heart Failure due to Systolic Dysfunction Complicating Acute Myocardial Infarction. Eplerenone Post-AMI Heart Failure Efficacy and Survival Study. Cardiovasc Drugs Ther. 2001;15(1):79-87. doi: 10.1023/a:1011119003788.

30. Serenelli M, Jackson A, Dewan P, Jhund PS, Petrie MC, Rossignol P, et al. Mineralocorticoid Receptor Antagonists, Blood Pressure, and Outcomes in Heart Failure With Reduced Ejection Fraction. JACC Heart Fail. 2020;8(3):188-98. doi: 10.1016/j.jchf.2019.09.011.

31. Kapelios CJ, Lund LH, Benson L, Dahlström U, Rosano GMC, Hauptman PJ, et al. Digoxin use in Contemporary Heart Failure with Reduced Ejection Fraction: An Analysis from the Swedish Heart Failure Registry. Eur Heart J Cardiovasc Pharmacother. 2021:pvab079. doi: 10.1093/ehjcvp/pvab079.

32. Hollenberg SM, Stevenson LW, Ahmad T, Amin VJ, Bozkurt B, Butler J, et al. 2019 ACC Expert Consensus Decision Pathway on Risk Assessment, Management, and Clinical Trajectory of Patients Hospitalized With Heart Failure: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2019;74(15):1966-2011. doi: 10.1016/j.jacc.2019.08.001.

33. Zhou J, Cao J, Jin X, Zhou J, Chen Z, Xu D, et al. Digoxin is Associated with Worse Outcomes in Patients with Heart Failure with Reduced Ejection Fraction. ESC Heart Fail. 2020;7(1):138-46. doi: 10.1002/ehf2.12539.

34. Malik A, Masson R, Singh S, Wu WC, Packer M, Pitt B, et al. Digoxin Discontinuation and Outcomes in Patients With Heart Failure with Reduced Ejection Fraction. J Am Coll Cardiol. 2019;74(5):617-27. doi: 10.1016/j.jacc.2019.05.064.

35. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, et al. Ivabradine and Outcomes in chronic Heart Failure (SHIFT): A Randomised Placebo-Controlled Study. Lancet. 2010;376(9744):875-85. doi: 10.1016/S0140-6736(10)61198-1.

36. Pereira-Barretto AC. Cardiac and Hemodynamic Benefits: Mode of Action of Ivabradine in Heart Failure. Adv Ther. 2015;32(10):906-19. doi: 10.1007/s12325-015-0257-6.

37. Reil JC, Tardif JC, Ford I, Lloyd SM, O'Meara E, Komajda M, et al. Selective Heart Rate Reduction with Ivabradine Unloads the Left Ventricle in Heart Failure Patients. J Am Coll Cardiol. 2013;62(21):1977-85. doi: 10.1016/j.jacc.2013.07.027.

38. Elzeneini M, Aranda JM Jr, Al-Ani M, Ahmed MM, Parker AM, Vilaro JR. Hemodynamic Effects of Ivabradine use in Combination with Intravenous Inotropic Therapy in Advanced Heart Failure. Heart Fail Rev. 2021;26(2):355-61. doi: 10.1007/s10741-020-10029-x.

39. Pieske B, Maier LS, Piacentino V 3rd, Weisser J, Hasenfuss G, Houser S. Rate Dependence of [Na+]i and Contractility in Nonfailing and failing Human Myocardium. Circulation. 2002;106(4):447-53. doi: 10.1161/01.cir.0000023042.50192.f4.

40. Cavusoglu Y, Mert U, Nadir A, Mutlu F, Morrad B, Ulus T. Ivabradine Treatment Prevents Dobutamine-Induced Increase in Heart Rate in Patients with Acute Decompensated Heart Failure. J Cardiovasc Med. 2015;16(9):603-9. doi: 10.2459/JCM.0000000000000033.

41. Gallet R, Ternacle J, Damy T, Guendouz S, Bremont C, Seemann A, et al. Hemodynamic Effects of Ivabradine in Addition to Dobutamine in Patients with Severe Systolic Dysfunction. Int J Cardiol. 2014;176(2):450-5. doi: 10.1016/j.ijcard.2014.07.093.

42. Rosano GMC, Allen LA, Abdin A, Lindenfeld J, O'Meara E, Lam CSP, et al. Drug Layering in Heart Failure: Phenotype-Guided Initiation. JACC Heart Fail. 2021;9(11):775-83. doi: 10.1016/j.jchf.2021.06.011.

43. Teerlink JR, Felker GM, McMurray JJ, Solomon SD, Adams KF Jr, Cleland JG, et al. Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure (COSMIC-HF): A Phase 2, Pharmacokinetic, Randomised, Placebo-Controlled Trial. Lancet. 2016;388(10062):2895-903. doi: 10.1016/S0140-6736(16)32049-9.

44. Teerlink JR, Diaz R, Felker GM, McMurray JJV, Metra M, Solomon SD, et al. Cardiac Myosin Activation with Omecamtiv Mecarbil in Systolic Heart Failure. N Engl J Med. 2021;384(2):105-16. doi: 10.1056/NEJMoa2025797.

45. Teerlink JR, Diaz R, Felker GM, McMurray JJV, Metra M, Solomon SD, et al. Effect of Ejection Fraction on Clinical Outcomes in Patients Treated With Omecamtiv Mecarbil in GALACTIC-HF. J Am Coll Cardiol. 2021;78(2):97-108. doi: 10.1016/j.jacc.2021.04.065.

46. Armstrong PW, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J, et al. Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2020;382(20):1883-93. doi: 10.1056/NEJMoa1915928.

47. Dounaevskaia V, Yan AT, Charytan D, dimeglio L, Leong-Poi H, Al-Hesayen A, Goldstein MB, Wald R. The Management of Left Ventricular Systolic Dysfunction in Patients with Advanced Chronic Kidney Disease. J Nephrol. 2011;24(1):41-9. doi: 10.5301/jn.2010.1871.

48. Berger AK, Duval S, Manske C, Vazquez G, Barber C, Miller L, et al. Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers in Patients with Congestive Heart Failure and Chronic Kidney Disease. Am Heart J. 2007;153(6):1064-73. doi: 10.1016/j.ahj.2007.03.017.

49. Heywood JT, Fonarow GC, Yancy CW, Albert NM, Curtis AB, Stough WG, et al. Influence of Renal Function on the use of Guideline-Recommended Therapies for Patients with Heart Failure. Am J Cardiol. 2010;105(8):1140-6. doi: 10.1016/j.amjcard.2009.12.016.

50. Kottgen A, Russell SD, Loehr LR, Crainiceanu CM, Rosamond WD, Chang PP, et al. Reduced Kidney Function as a Risk Factor for Incident Heart Failure: The Atherosclerosis Risk in Communities (ARIC) Study. J Am Soc Nephrol. 2007;18(4):1307-15. doi: 10.1681/ASN.2006101159.

51. Clark H, Krum H, Hopper I. Worsening Renal Function During Renin-Angiotensin-Aldosterone System Inhibitor Initiation and Long-Term Outcomes in Patients with leFt Ventricular Systolic Dysfunction. Eur J Heart Fail. 2014;16(1):41-8. doi: 10.1002/ejhf.13.

52. Edner M, Benson L, Dahlström U, Lund LH. Association Between Renin-Angiotensin System Antagonist use and Mortality in Heart Failure with Severe Renal Insufficiency: A Prospective Propensity Score-Matched Cohort Study. Eur Heart J. 2015;36(34):2318-26. doi: 10.1093/eurheartj/ehv268.

53. Damman K, Gori M, Claggett B, Jhund PS, Senni M, Lefkowitz MP, et al. Renal Effects and Associated Outcomes During Angiotensin-Neprilysin Inhibition in Heart Failure. JACC Heart Fail. 2018;6(6):489-98. doi: 10.1016/j.jchf.2018.02.004.

54. Zannad F, Ferreira JP, Pocock SJ, Zeller C, Anker SD, Butler J, et al. Cardiac and Kidney Benefits of Empagliflozin in Heart Failure Across the Spectrum of Kidney Function: Insights From EMPEROR-Reduced. Circulation. 2021;143(4):310-21. doi: 10.1161/CIRCULATIONAHA.120.051685.

55. Jhund PS, Solomon SD, Docherty KF, Heerspink HJL, Anand IS, Böhm M, et al. Efficacy of Dapagliflozin on Renal Function and Outcomes in Patients With Heart Failure With Reduced Ejection Fraction: Results of DAPA-HF. Circulation. 2021;143(4):298-309. doi: 10.1161/CIRCULATIONAHA.120.050391.

56. Kristensen SL, Docherty KF, Jhund PS, Bengtsson O, Demets DL, Inzucchi SE, et al. Dapagliflozin Reduces the Risk of Hyperkalaemia in Patients with Heart Failure and Reduced Ejection Fraction: A Secondary Analysis DAPA-HF. Eur Heart J. 2020;41(Suppl 2):ehaa946.0939. doi: 10.1093/ehjci/ehaa946.0939.

57. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. 2013 ACCF/AHA guideline for the Management of Heart Failure: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;128(16):240-327. doi: 10.1161/CIR.0b013e31829e8776.

58. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney inter.2013;3(1):1-150. doi: 10.1038/kisup.2012.73.

59. Epstein M, Reaven NL, Funk SE, McGaughey KJ, Oestreicher N, Knispel J. Evaluation of the Treatment Gap Between Clinical Guidelines and the Utilization of Renin-Angiotensin-Aldosterone System Inhibitors. Am J Manag Care. 2015;21(11 Suppl):212-20.

60. Beusekamp JC, Tromp J, van der Wal HH, Anker SD, Cleland JG, Dickstein K, et al. Potassium and the Use of Renin-Angiotensin-Aldosterone System Inhibitors in Heart Failure with Reduced Ejection Fraction: Data from BIOSTAT-CHF. Eur J Heart Fail. 2018;20(5):923-30. doi: 10.1002/ejhf.1079.

61. Lund LH, Pitt B. Is hyperkalaemia in Heart Failure a Risk Factor or a Risk Marker? Implications for Renin-Angiotensin-Aldosterone System Inhibitor Use. Eur J Heart Fail. 2018;20(5):931-2. doi: 10.1002/ejhf.1175.

62. Ferreira JP, Butler J, Rossignol P, Pitt B, Anker SD, Kosiborod M, et al. Abnormalities of Potassium in Heart Failure: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020;75(22):2836-50. doi: 10.1016/j.jacc.2020.04.021.

63. Desai AS, Vardeny O, Claggett B, McMurray JJ, Packer M, Swedberg K, et al. Reduced Risk of Hyperkalemia During Treatment of Heart Failure With Mineralocorticoid Receptor Antagonists by Use of Sacubitril/Valsartan Compared With Enalapril: A Secondary Analysis of the PARADIGM-HF Trial. JAMA Cardiol. 2017;2(1):79-85. doi: 10.1001/jamacardio.2016.4733.

64. Pitt B, Anker SD, Bushinsky DA, Kitzman DW, Zannad F, Huang IZ, et al. Evaluation of the Efficacy and Safety of RLY5016, a Polymeric Potassium Binder, in a Double-Blind, Placebo-Controlled Study in Patients with Chronic Heart Failure (the PEARL-HF) Trial. Eur Heart J. 2011;32(7):820-8. doi: 10.1093/eurheartj/ehq502.

65. Pharithi RB, Ferre-Vallverdu M, Maisel AS, O'Connell E, Walshe M, Sweeney C, et al. Sacubitril-Valsartan in a Routine Community Population: Attention to Volume Status Critical to Achieving Target Dose. ESC Heart Fail. 2020;7(1):158-66. doi: 10.1002/ehf2.12547.

66. Kittleson M, Hurwitz S, Shah MR, Nohria A, Lewis E, Givertz M, Fet al. Development of Circulatory-Renal Limitations to Angiotensin-Converting Enzyme Inhibitors Identifies Patients with Severe Heart Failure and Early Mortality. J Am Coll Cardiol. 2003;41(11):2029-35. doi: 10.1016/s0735-1097(03)00417-0.

67. Sackner-Bernstein JD. Use of Carvedilol in Chronic Heart Failure: Challenges in Therapeutic Management. Prog Cardiovasc Dis. 1998;41(1 Suppl 1):53-8. doi: 10.1016/s0033-0620(98)80031-5.

68. Butler J, Khadim G, Belue R, Chomsky D, Dittus RS, Griffin M, et al. Tolerability to Beta-Blocker Therapy Among Heart Failure Patients in Clinical Practice. J Card Fail. 2003;9(3):203-9. doi: 10.1054/jcaf.2003.34.

69. Lam PH, Packer M, Fonarow GC, Faselis C, Allman RM, Morgan CJ, et al. Early Effects of Starting Doses of Enalapril in Patients with Chronic Heart Failure in the SOLVD Treatment Trial. Am J Med. 2020;133(2):25-31. doi: 10.1016/j.amjmed.2019.06.053.

70. Krum H, Roecker EB, Mohacsi P, Rouleau JL, Tendera M, Coats AJ, et al. Effects of Initiating Carvedilol in Patients with Severe Chronic Heart Failure: Results from the COPERNICUS Study. JAMA. 2003;289(6):712-8. doi: 10.1001/jama.289.6.712.

71. Pitt B, White H, Nicolau J, Martinez F, Gheorghiade M, Aschermann M, et al. Eplerenone Reduces Mortality 30 Days After Randomization Following Acute Myocardial Infarction in Patients with Left Ventricular Systolic Dysfunction and Heart Failure. J Am Coll Cardiol. 2005;46(3):425-31. doi: 10.1016/j.jacc.2005.04.038.

72. Konstam MA, Neaton JD, Dickstein K, Drexler H, Komajda M, Martinez FA, et al. Effects of High-Dose versus Low-Dose Losartan on Clinical Outcomes in Patients with Heart Failure (HEAAL study): A Randomised, Double-Blind Trial. Lancet. 2009;374(9704):1840-8. doi: 10.1016/S0140-6736(09)61913-9.

73. Vardeny O, Claggett B, Packer M, Zile MR, Rouleau J, Swedberg K, et al. Efficacy of Sacubitril/Valsartan vs. Enalapril at Lower than Target doses in Heart Failure with Reduced Ejection Fraction: The PARADIGM-HF Trial. Eur J Heart Fail. 2016;18(10):1228-34. doi: 10.1002/ejhf.580.

74. Packer M, McMurray JJV. Rapid Evidence-Based Sequencing of Foundational Drugs for Heart Failure and a Reduced Ejection Fraction. Eur J Heart Fail. 2021;23(6):882-94. doi: 10.1002/ejhf.2149.

75. Bhatt AS, Abraham WT, Lindenfeld J, Bristow M, Carson PE, Felker GM, et al. Treatment of HF in an Era of Multiple Therapies: Statement From the HF Collaboratory. JACC Heart Fail. 2021;9(1):1-12. doi: 10.1016/j.jchf.2020.10.014.

76. Stevenson LW, Perloff JK. The Limited Reliability of Physical Signs for Estimating Hemodynamics in Chronic Heart Failure. JAMA. 1989;261(6):884-8.

77. Stevenson LW. Design of Therapy for Advanced Heart Failure. Eur J Heart Fail. 2005;7(3):323-31. doi: 10.1016/j.ejheart.2005.01.004.

Overlapping Etiologies in a Young Patient with Severe Myocarditis: A Case Report

Thaís Martins de Oliveira,[1] Fernando Luis Scolari,[2] Fabiano de Oliveira Poswar,[1] Francine Hehn de Oliveira,[3] Ricardo Stein,[4,5] Lívia Adams Goldraich[2,4]

Serviço de Genética, Hospital de Clínicas de Porto Alegre,[1] Porto Alegre, RS – Brazil

Equipe de Insuficiência Cardíaca e Transplante Cardíaco, Serviço de Cardiologia, Hospital de Clínicas de Porto Alegre,[2] Porto Alegre, RS – Brazil

Serviço de Patologia Cirúrgica, Hospital de Clínicas de Porto Alegre,[3] Porto Alegre, RS – Brazil

Programa de Pós-Graduação em Cardiologia e Ciências Cardiovasculares, Universidade Federal do Rio Grande do Sul,[4] Porto Alegre, RS – Brazil

Departamento de Medicina Interna da Universidade Federal do Rio Grande do Sul,[5] Porto Alegre, RS – Brazil

Introduction

Etiological identification of young patients with heart failure should always be a medical goal. In this scenario, infectious myocarditis is a possible diagnosis and, when it occurs, it has a benign course in the majority of cases. However, congenital heart diseases or familial forms of cardiomyopathy should be considered in differential diagnosis and/or concomitantly, particularly in more severe presentations of myocarditis. In these cases, in addition to specific investigation for myocarditis, which may include clinical evaluation, imaging exams, laboratory tests, and endomyocardial biopsy with viral agent testing in myocardial tissue, genetic study is also worth considering.[1] Associated etiologies can have an impact on clinical presentation and evolution, but data are still scarce,[2] which means that there is still a gap to be explored in the literature. In this report, we describe the case of a young man with cardiogenic shock secondary to myocarditis caused by Epstein Barr virus (EBV), which led to identification of a pathogenic mutation in the *PKP2* gene.

Case Report

A 17-year-old male patient, with no previous comorbidities, sought emergency care, reporting dyspnea and retrosternal pain during exercise, rapidly progressing to syncope and cardiogenic shock. He required vasopressors, inotropes, and invasive mechanical ventilatory support. Electrocardiogram showed ST-segment elevation in leads V1, V2, and aVR, as well as ST depression in the other leads, which were not characteristic of acute coronary syndrome. Echocardiogram showed increased left atrial volume (41 mL/m^2), left ventricular dilation (59/51 mm), and systolic dysfunction with ejection fraction of 26%. Apical intracavitary thrombus was identified and treated with anticoagulation. Due to clinical suspicion of myocardial inflammation, cardiac magnetic resonance imaging (MRI) was performed, identifying typical signs of acute myocarditis with edema, hyperemia, and delayed enhancement, which was non-ischemic, affecting 45% of the left ventricle (Figure 1A). Antibiotic therapy was initiated due to fever and leukocytosis, but the regimen was suspended after 5 days due to negative blood cultures. Serological evaluation identified recent EBV infection, corroborating the diagnostic hypothesis of viral myocarditis. There was clinical improvement, making it possible to reduce support. The patient had a marked elevation in ultrasensitive troponin I, which remained elevated for a prolonged period: 9,411 ng/L upon admission; 14,760 ng/L peak; and 31.51 ng/L after 30 days.

The patient showed partial improvement in ventricular function at 3 months after discharge from the hospital (ejection fraction 42% with left ventricular dilatation). A second cardiac MRI performed 6 months later demonstrated regression of inflammatory activity, but late enhancement persisted (Figure 1B). In spite of optimized pharmacological therapy with sacubitril-valsartan, metoprolol, and spironolactone, as well as good functional capacity assessed directly by ergospirometry (peak oxygen uptake 34.4 mL^{-1}.kg^{-1}.min), after 1 year of follow-up, elevated troponin, left ventricular dilatation, and moderate systolic dysfunction persisted. The decision was made to implant a cardioverter-defibrillator after a new episode of syncope during recovery from physical exercise, which the patient had been allowed to do. Endomyocardial biopsy with viral testing 24 months after presentation and histopathology identified mild tissue edema, areas of nuclear hypertrophy, and absence of lymphocytic infiltrate on hematoxylin-eosin, but there was lymphocyte activation on immunohistochemistry (Figure 1C). The presence of EBV in the myocardial tissue was identified by qualitative PCR, but not by EBER *in situ* hybridization. Testing for other viral agents (enterovirus, herpes type 6, parvovirus B19, herpes simplex 1 and 2, adenovirus, and cytomegalovirus) was negative.

As the disease had a very prolonged course with intense fibrosis, the decision was made to carry out complementary genetic study (panel of 168 genes for cardiomyopathies). Molecular analysis of the index case (proband) identified a pathogenic variant, c.1440_1444del, (p.Asn480Lysfs*20), in the *PKP2* gene, NM_004572.3 (Invitae Arrhythmia and Cardiomyopathy Comprehensive Panel, Invitae Corp, San

Keywords

Inflammation; Myocardial Injury; Genetics; Arrhythmogenic Cardiomyopathy.

Mailing Address: Livia Adams Goldraich •
Hospital de Clínicas de Porto Alegre - Rua Ramiro Barcelos, 2350, sala 2060. Postal Code 90035-903, Porto Alegre, RS - Brazil
E-mail: lgoldraich@hcpa.edu.br
Manuscript received February 03, 2022, revised manuscript February 14, 2022, accepted March 01, 2022

DOI: https://doi.org/10.36660/abchf.20220022

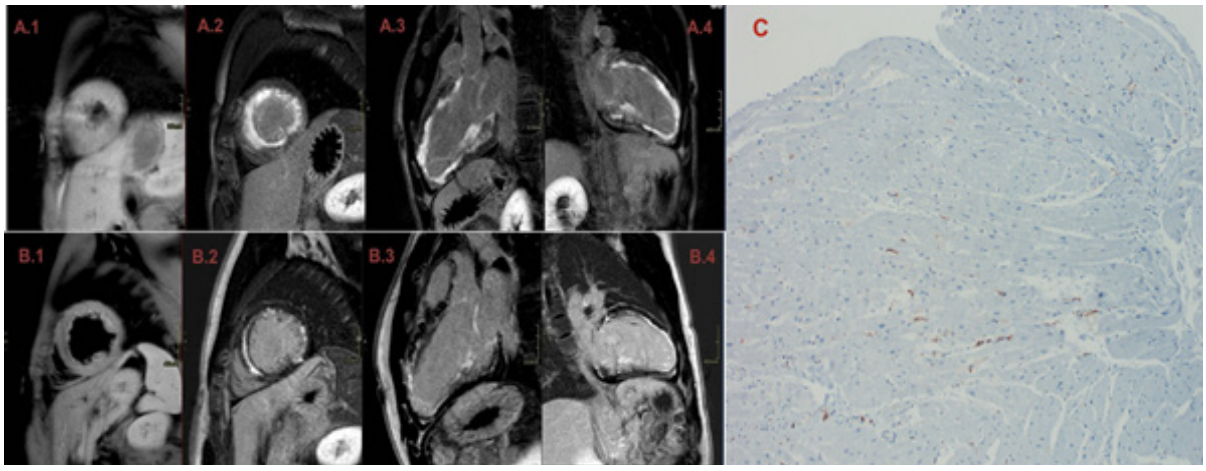


Figure 1 – *A) First cardiac MRI performed. A.1) T2 with fat saturation demonstrating diffuse myocardial edema. A.2) Delayed enhancement in the short axis demonstrating diffuse subendocardial and mesocardial uptake, without defined coronary territory. A.3) Late enhancement in the 3-camera plane demonstrating diffuse subendocardial and mesocardial uptake, without defined coronary territory, including involvement of the papillary muscles. A.4) Delayed enhancement in the 2-camera plane demonstrating diffuse subendocardial and mesocardial uptake, without defined coronary territory. B) Cardiac MRI 6 months after the cardiac MRI in Figure 1A. B.1) T2 with fat saturation in the absence of edema. B.2) Delayed enhancement in the short axis demonstrating ventricular dilatation and reduced uptake, with fine diffuse mesocardial and subendocardial areas of involvement. B.3) Late enhancement in the 3-chamber plane demonstrating ventricular dilatation and reduced uptake, with fine diffuse mesocardial and subendocardial areas of involvement. B.4) Delayed enhancement in the 2-chamber plane demonstrating ventricular dilatation and reduced uptake, with fine diffuse mesocardial and subendocardial areas of involvement. C) Immunohistochemistry showing evidence of lymphocyte activation (CD4-positive).*

Francisco, CA, USA). This variant has a deletion of 3 amino acids, and this deletion promotes the appearance of a premature stop codon, generating a truncated protein. Thus, this messenger DNA undergoes a process called decay and is not transcribed, leading to a lack of this protein. When producing the family genogram, it was possible to observe that several family members were at risk of having inherited the mutation in question (Figure 2).

Discussion

We have reported the case of a young patient with cardiogenic shock due to acute viral myocarditis caused by EBV. Viral agent testing in the tissue demonstrated persistence of the etiologic agent 24 months after presentation. Due to the severity of the clinical condition and the finding of late enhancement on cardiac MRI, a genetic panel of 168 genes for cardiomyopathies was performed, identifying an underlying arrhythmogenic cardiomyopathy due to a pathogenic mutation in the *PKP2* gene.

Myocarditis is an inflammatory heart muscle disease triggered by infectious agents, toxic substances, and/or immune activation.[3] The presentation and clinical evolution are varied, from spontaneous resolution to progression to severe heart failure.[4] Myocarditis caused by EBV, however, is rare.[5] Previous reports have described viral symptoms (fever, prostration, and myalgia) associated with cardiac manifestations such as dyspnea, chest pain, electrocardiography changes, and ventricular arrhythmias.[6] The magnitude of late enhancement in the left ventricle, however, was lower in other series (4% to 10% of left ventricular mass) than in our patient (45%).[6] Our hypothesis is that the identification of a pathogenic desmosomal mutation may have been determinant to the findings in this case (in particular the extent of late enhancement). It is important to underscore that doubts still persist regarding the benefit of treatment with antiviral drugs and immunosuppressive therapy in cases where myocardial inflammatory signs persist in spite of viral elimination.[6]

In turn, arrhythmogenic cardiomyopathy is an inherited disease characterized by myocardial liposubstitution and interstitial fibrosis. It is expressed by means of ventricular arrhythmias, and it may progress with ventricular dilation and heart failure. This pathology increases the risk of sudden death, which may be the first clinical manifestation. However, it has incomplete penetrance and variable clinical presentation.[7] Most mutations have been described in desmosomal genes, *PKP2* being the most frequent.[8] Loss of PKP2 protein expression disrupts sodium channel traffic in the intercalated disc, facilitating the emergence of arrhythmias.[9]

Although previously asymptomatic, the presence of structural left ventricular changes may have predisposed the tropism of EBV to the myocardium.[2] In fact, a higher prevalence of cardiotropic viruses has been described in patients with arrhythmogenic cardiomyopathy. Furthermore, the occurrence of viral infections may play a role in disease progression, contributing to morbidity and mortality.[10] Finally, inflammation plays a central role in the pathophysiology of arrhythmogenic cardiomyopathy, and the presence of lymphocytic infiltrates is a common finding, even when there is no viral genome identification. In some cases, the active

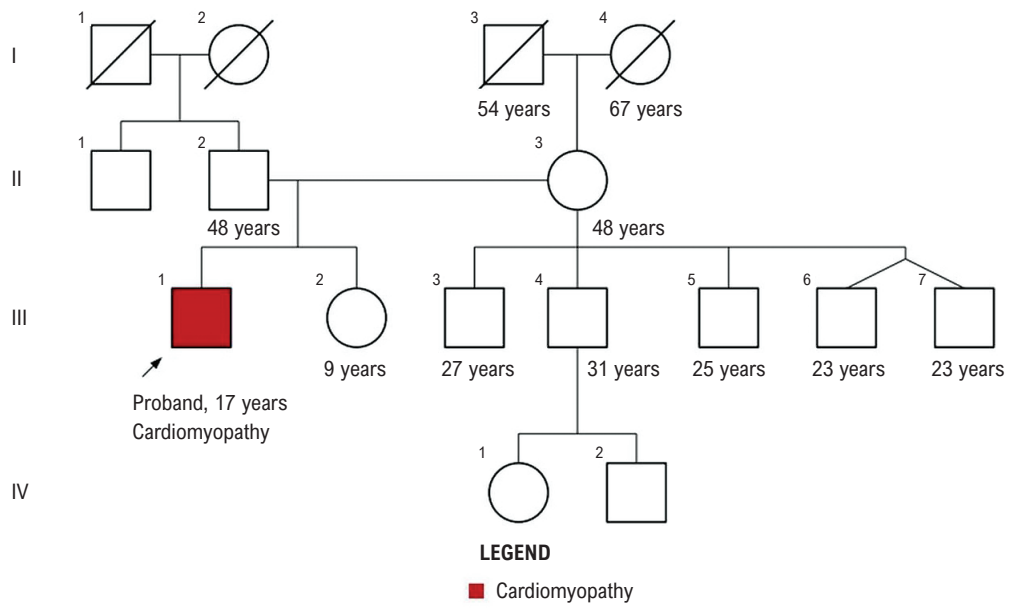


Figure 2 – *Genogram. Note that patients III.2, III.3, III.4, III.5, III.6, and III.7 were at a 50% risk of having inherited a pathogenic variant in the event that patient II.3 was heterozygous.*

phase of the disease may present as clinical myocarditis, which reinforces the very probable overlap between both conditions.[11]

Conclusion

We have reported the case of a young patient admitted for cardiogenic shock caused by EBV myocarditis, who was also the carrier of a pathogenic mutation in the *PKP2* gene, which is the one most frequently involved in familial arrhythmogenic cardiomyopathy. Severe presentations of myocarditis caused by infectious agents can occur in parallel with different hereditary cardiomyopathies and, in these cases, cascade screening and family genetic counseling can assist in therapeutic management from the perspective of the best available evidence allied with the emerging concept of personalized medicine.

Author Contributions

Conception and design of the research: Oliveira TM, Goldraich LA; Acquisition of data: Oliveira TM, Oliveira FH; Analysis and interpretation of the data: Oliveira TM, Scolari FL, Poswar FO, Oliveira FH, Stein R; Writing of the manuscript: Oliveira TM, Scolari FL, Poswar FO, Goldraich LA; Critical revision of the manuscript for intellectual contente: Scolari FL, Poswar FO, Stein R, Goldraich LA.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Wong CM, Hawkins NM, Petrie MC, Jhund PS, Gardner RS, Ariti CA, et al. Heart Failure in Younger Patients: The Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC). Eur Heart J. 2014;35(39):2714-21. doi: 10.1093/eurheartj/ehu216. Epub 2014 Jun 17. PMID: 24944329..
2. Campuzano O, Fernández-Falgueras A, Sarquella-Brugada G, Sanchez O, Cesar S, Mademont I, et al. A Genetically Vulnerable Myocardium May Predispose to Myocarditis. J Am Coll Cardiol. 2015;66(25):2913-14. doi: 10.1016/j.jacc.2015.10.049.

3. Pollack A, Kontorovich AR, Fuster V, Dec GW. Viral Myocarditis--Diagnosis, Treatment Options, and Current Controversies. Nat Rev Cardiol. 2015;12(11):670-80. doi: 10.1038/nrcardio.2015.108.

4. Ammirati E, Frigerio M, Adler ED, Basso C, Birnie DH, Brambatti M, et al. Management of Acute Myocarditis and Chronic Inflammatory Cardiomyopathy: An Expert Consensus Document. Circ Heart Fail. 2020;13(11):e007405. doi: 10.1161/CIRCHEARTFAILURE.120.007405.

5. Roubille F, Gahide G, Moore-Morris T, Granier M, Davy JM, Vernhet H, et al. Epstein Barr Virus (EBV) and Acute Myopericarditis in an Immunocompetent Patient: First Demonstrated Case and Discussion. Intern Med. 2008;47(7):627-9. doi: 10.2169/internalmedicine.47.0691.

6. Mavrogeni S, Spargias K, Bratis C, Kolovou G, Papadopoulou E, Pavlides G. EBV INFECTION as a Cause of VT: Evaluation by CMR. JACC Cardiovasc Imaging. 2011;4(5):561-2. doi: 10.1016/j.jcmg.2010.11.022.

7. Svensson A, Platonov PG, Haugaa KH, Zareba W, Jensen HK, Bundgaard H, et al. Genetic Variant Score and Arrhythmogenic Right Ventricular Cardiomyopathy Phenotype in Plakophilin-2 Mutation Carriers. Cardiology. 2021;146(6):763-71. doi: 10.1159/000519231.

8. van Opbergen CJM, Noorman M, Pfenniger A, Copier JS, Vermij SH, Li Z, van der Nagel R, et al. Plakophilin-2 Haploinsufficiency Causes Calcium Handling Deficits and Modulates the Cardiac Response Towards Stress. Int J Mol Sci. 2019;20(17):4076. doi: 10.3390/ijms20174076.

9. Novelli V, Malkani K, Cerrone M. Pleiotropic Phenotypes Associated With PKP2 Variants. Front Cardiovasc Med. 2018;5:184. doi: 10.3389/fcvm.2018.00184.

10. Fontaine G, Fontaliran F, Andrade FR, Velasquez E, Tonet J, Jouven X, et al. The Arrhythmogenic Right Ventricle. Dysplasia versus Cardiomyopathy. Heart Vessels. 1995;10(5):227-35. doi: 10.1007/BF01744901.

11. Lopez-Ayala JM, Pastor-Quirante F, Gonzalez-Carrillo J, Lopez-Cuenca D, Sanchez-Munoz JJ, Oliva-Sandoval MJ, et al. Genetics of Myocarditis in Arrhythmogenic Right Ventricular Dysplasia. Heart Rhythm. 2015;12(4):766-73. doi: 10.1016/j.hrthm.2015.01.001.

Case Report

Symptomatic Acute Myopericarditis after Pfizer Vaccine against COVID-19

Ivana Tabalipa Giublin,[1] *Camila Hartmann,*[1,2] *Otavio Celeste Mangili,*[3] *Afonso Akio Shiozaki,*[4] *Lídia Ana Zytynski Moura*[1,2]

Hospital Marcelino Champagnat,[1] *Curitiba, PR – Brazil*
Pontifícia Universidade Católica do Paraná (PUCPR),[2] *Curitiba, PR – Brazil*
Professor Associado de Cardiologia da Uningá,[3] *Maringá, PR – Brazil*
Centro de Diagnósticos Hospital Paraná (Unitom/DASA),[4] *Maringá, PR – Brazil*

Introduction

Cases of myocarditis and pericarditis have been reported in diverse parts of the world since vaccination against the new coronavirus began with messenger RNA (mRNA) vaccines, mainly those produced by Pfizer-BioNTech.[1] The pathophysiology of this vaccine-induced pathology is not yet fully understood, but it may be related to the active component of the vaccine (the mRNA sequence that encodes the SARS-CoV-2 spike protein) or to the immune system response that is triggered after vaccination[2]. What is known so far is that it is a rare adverse event in view of the number of people who have already been immunized with these components, and the vast majority of cases reported in the literature have a benign course, with good evolution.[1-10] We report a case of myopericarditis in a young adult who presented symptoms 2 days after receiving the second dose of the Pfizer vaccine against COVID-19.

Case Report

JASD, a male, 18-year-old patient, with a history of leukemia treated in childhood, developed intense chest pain, radiating to the left upper limb, as well as back pain, 2 days after receiving the second dose of the Pfizer vaccine against COVID-19. Upon hospitalization for investigation in his hometown, his electrocardiogram showed ST-segment elevation in the inferolateral wall, and there were changes in troponin I levels (6.33; reference value: 0 to 0.5) and CK-MB mass (98.4; reference value: 0 to 7.0). Cardiac magnetic resonance imaging was performed, demonstrating the presence of late enhancement (edema/necrosis), with non-coronary and mesoepicardial enhancement in the entire lateral wall, as well as in the apical portion of the inferior, septal, and apex walls of the left ventricle, suggestive of myocarditis. Additionally, areas of edema and delayed enhancement were observed over the posterior pericardium, although there was no pericardial thickening. After 48 hours of hospitalization, the patient presented a new worsening of chest pain, tachycardia, and an increase in myocardial necrosis markers, leading to the decision to perform resonance imaging again for therapeutic definition. The second examination demonstrated the appearance of new areas of late enhancement, in the middle and basal portions of the inferior and inferoseptal walls, as well as an increase in the segments with hypersignal with myocardial edema, indicating extension of the areas of myocardial necrosis resulting from clearly active myocarditis (Figures 1 and 2). The decision was made to initiate pulse therapy with 1 g of methylprednisolone daily and to transfer the patient to the cardiological intensive care unit of a tertiary hospital, due to the risk of progression to fulminant myocarditis. In this unit, the previously initiated therapeutic regimen (enalapril, bisoprolol, colchicine, and methylprednisolone) was maintained. Troponin I measured on admission to this hospital was significantly altered (416.5; reference value in this hospital: less than 19.8), and there was a slight change in the inflammatory marker (C-reactive protein: 7.9; reference value: less than 5.0). Electrocardiogram showed changes in ventricular repolarization in the inferior wall and slow progression of the R wave, as well as ST-segment elevation in the anterior wall. The transthoracic echocardiogram was normal. The patient had transient episodes of pulmonary congestion, bradycardia, and elevated lactate levels, but all of these were easy to manage and resolve. He did not have any new episodes of chest pain after admission to this hospital, and he evolved with a drop in C-reactive protein and troponin I. After completing pulse therapy with corticosteroids for a 3-day period, resonance imaging was repeated to reassess the extent of injury, which showed improvement in relation to the last exam that had been performed in his hometown. The patient evolved with clinical stability and significant improvement. He was discharged after 6 days, with a prescription for bisoprolol, enalapril, spironolactone, and colchicine. He was further instructed to avoid physical exertion for a minimum period of 6 months, to undergo outpatient Holter, and to return early to the assistant cardiologist in his hometown.

Keywords

Myocarditis; Pericarditis; COVID-19 Vaccines

Mailing Address: Ivana Tabalipa Giublin •
Avenida Presidente Affonso Camargo, 1.399. Postal Code 80050-370, Cristo Rei, Curitiba, PR - Brazil
E-mail: ivanagiublin@gmail.com
Manuscript received January 21, 2022, revised manuscript February 01, 2022, accepted February 22, 2022

DOI: https://doi.org/10.36660/abchf.20220023

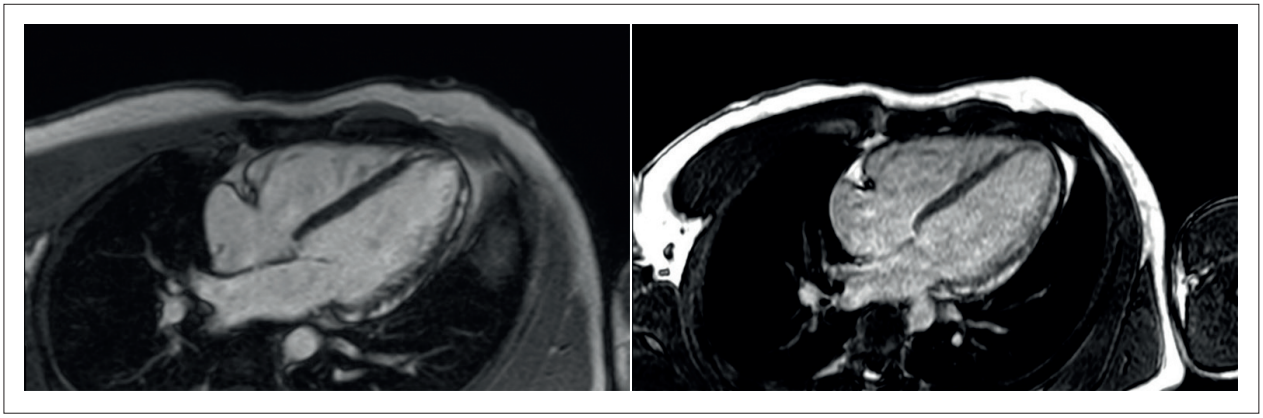


Figure 1 – *Cardiac magnetic resonance imaging showing late enhancement. Image 1: first exam; image 2: exam performed 48 hours later.*

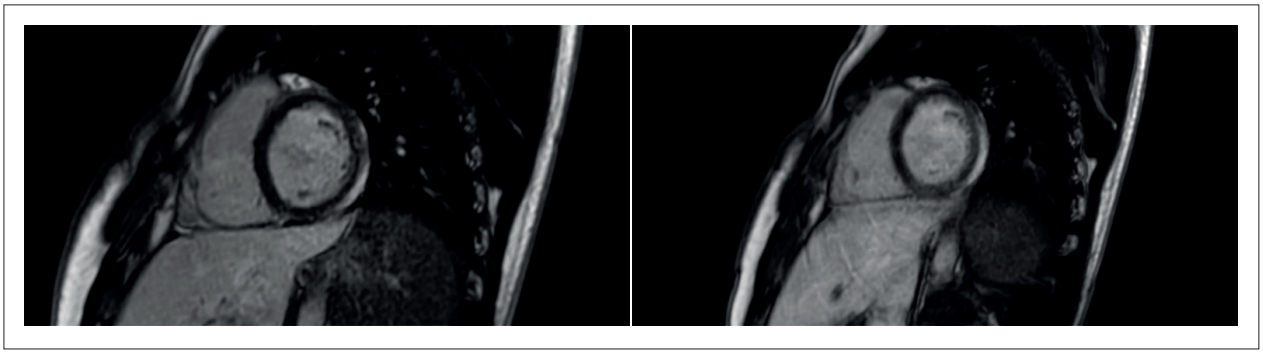


Figure 2 – *Cardiac magnetic resonance imaging showing late enhancement. Image 1: first exam; image 2: exam performed 48 hours later.*

Discussion

Repeated case descriptions seem to suggest a new adverse event associated with mRNA vaccines, namely, post-vaccination myocarditis and pericarditis, which had not been observed in the initial studies published by the pharmaceutical company in December 2020.11 The occurrence seems to be more common in young male adults. In the initial clinical trials of mRNA vaccines, systemic adverse reactions were also observed more frequently in this population, probably due to increased immunogenicity.[9,11] A systematic review that evaluated cardiac complications in this scenario, including 43 case reports and 26 series, identified that myocarditis/myopericarditis and pericarditis were the most common adverse events among the 243 complications reported, and they were observed more after the Pfizer mRNA vaccine.[1] The majority of patients are previously healthy, and the symptoms are typical of myocarditis and pericarditis due to other causes, with chest pain being the most reported symptom, followed by fever. They generally start within a week of the second dose of the vaccine. Electrocardiographic changes (such as ST-segment changes) are present in the vast majority of cases, as are increased troponin and increased inflammatory markers (such as C-reactive protein and erythrocyte sedimentation rate). The type of troponin used has been heterogeneous among the studies. A transthoracic echocardiogram with a normal result was common in several reports, but there were always changes on cardiac resonance imaging (in most cases, late enhancement with gadolinium, indicating myocardial necrosis/fibrosis). Before concluding diagnosis of post-vaccination myocarditis, the vast majority of patients underwent other exams to rule out other etiologies, including infection caused by the novel coronavirus. The most common situation is that patients present a mild condition with rapid recovery and short length of hospital stay.[1-10] As pharmacological treatment, they receive doses of non-steroidal anti-inflammatory drugs, colchicine, and corticosteroids. Some patients require intravenous immunoglobulin, acetylsalicylic acid, beta-blockers, and angiotensin-converting enzyme inhibitors due to left ventricular systolic dysfunction.[1,8] Most of the clinical information available on myocarditis after mRNA vaccination has been published in the form of case reports and series, making further studies necessary in order to establish these patients' long-term prognosis.

Conclusion

Although reports of myocarditis and pericarditis related to mRNA vaccines are becoming increasingly frequent in the literature, they are still considered rare in view of the number of individuals who are receiving these vaccines. Furthermore, the majority of cases have had a quick recovery, with good clinical evolution. Therefore, in spite of the real possibility of post-vaccination myocarditis, it is

still recommended to maintain the immunization schedule as a strategy to face the pandemic, seeing that the benefits of vaccination continue to outweigh the risks.

Acknowledgements

The authors would like to thank Dr. Otavio Celeste Mangili for referring the patient and the rest of the assisting team that accompanied the patient in Maringá, Paraná, Brazil. Thanks to the members of the Cardiac Intensive Care Unit at Hospital Marcelino Champagnat for providing medical services to the community and contributing to the development of a service of excellence. The authors would also like to thank the team responsible for admissions to the ward for working together on behalf of patients. Special thanks to the patients who place their trust in the hospital's multidisciplinary team, to take care of their health, making continuous improvement possible.

Author Contributions

Conception and design of the study, data acquisition, manuscript drafting: Giublin IT; critical revision for important intellectual content: Hartmann C, Moura LAZ; supervision as principal investigator: Mangili OC, Shiozaki AA, Moura LAZ.

Potential Conflicts of Interest

The authors declare no relevant conflicts of interest.

Sources of Funding

There were no external funding sources for this study.

Academic Affiliation

This study is not affiliated with any postgraduate programs.

Ethical Approval and Informed Consent

This article does not contain human or animal studies conducted by any of the authors.

References

1. Fazlollahi A, Zahmatyar M, Noori M, Nejadghaderi SA, Sullman MJM, Shekarriz-Foumani R, et al. Cardiac Complications Following mRNA COVID-19 Vaccines: A Systematic Review of Case Reports and Case Series. Rev Med Virol. 2021:e2318. doi: 10.1002/rmv.2318.
2. Mevorach D, Anis E, Cedar N, Bromberg M, Haas EJ, Nadir E, et al. Myocarditis After BNT162b2 mRNA Vaccine Against Covid-19 in Israel. N Engl J Med. 2021;385(23):2140-9. doi: 10.1056/NEJMoa2109730.
3. Matta A, Kunadharaju R, Osman M, Jesme C, McMiller Z, Johnson EM, et al. Clinical Presentation and Outcomes of Myocarditis Post mRNA Vaccination: A Meta-Analysis and Systematic Review. Cureus. 2021;13(11):e19240. doi: 10.7759/cureus.19240.
4. Cai C, Peng Y, Shen E, Huang Q, Chen Y, Liu P, et al. A Comprehensive Analysis of the Efficacy and Safety of COVID-19 Vaccines. Mol Ther. 2021;29(9):2794-805. doi: 10.1016/j.ymthe.2021.08.001.
5. Montgomery J, Ryan M, Engler R, Hoffman D, McClenathan B, Collins L, et al. Myocarditis Following Immunization with mRNA COVID-19 Vaccines in Members of the US Military. JAMA Cardiol. 2021;6(10):1202-6. doi: 10.1001/jamacardio.2021.2833.
6. Minocha PK, Better D, Singh RK, Hoque T. Recurrence of Acute Myocarditis Temporally Associated with Receipt of the mRNA Coronavirus Disease 2019 (COVID-19) Vaccine in a Male Adolescent. J Pediatr. 2021;238:321-3. doi: 10.1016/j.jpeds.2021.06.035.
7. Singh B, Kaur P, Cedeno L, Brahimi T, Patel P, Virk H, et al. COVID-19 mRNA Vaccine and Myocarditis. Eur J Case Rep Intern Med. 2021;8(7):002681. doi: 10.12890/2021_002681.
8. Bozkurt B, Kamat I, Hotez PJ. Myocarditis with COVID-19 mRNA Vaccines. Circulation. 2021;144(6):471-84. doi: 10.1161/CIRCULATIONAHA.121.056135.
9. Rosner CM, Genovese L, Tehrani BN, Atkins M, Bakhshi H, Chaudhri S, et al. Myocarditis Temporally Associated With COVID-19 Vaccination. Circulation. 2021;144(6):502-5. doi: 10.1161/CIRCULATIONAHA.121.055891.
10. Marshall M, Ferguson ID, Lewis P, Jaggi P, Gagliardo C, Collins JS, et al. Symptomatic Acute Myocarditis in 7 Adolescents After Pfizer-BioNTech COVID-19 Vaccination. Pediatrics. 2021;148(3):e2021052478. doi: 10.1542/peds.2021-052478.
11. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020;383(27):2603-15. doi: 10.1056/NEJMoa2034577.

Implementation of Home Use of Continuous Intravenous Inotrope as Palliative Therapy for a Patient with Advanced Heart Failure within the Brazilian Unified Health System: a Case Report

Ana Paula Chedid Mendes,[1] *Rita Zambonato,*[2] *Laura C. T. Hastenteufel,*[3] *Letícia Orlandin,*[3] *Nadine Clausell,*[3] *Livia Adams Goldraich*[3]

Hospital Universitário Antônio Pedro,[1] *Niterói, RJ – Brasil*

Programa de Cuidados Paliativos- Hospital de Clínicas de Porto Alegre,[2] *Porto Alegre, RS – Brasil*

Programa de Insuficiência Cardíaca e Transplante- Hospital de Clínicas de Porto Alegre,[3] *Porto Alegre, RS – Brasil*

Introduction

Contemporary evidence-based treatment has modified the natural history of heart failure (HF). Nevertheless, with the current aging of the population with HF and the elevated number of comorbidities, there is a large proportion of individuals who are ineligible for advanced therapies and who could potentially benefit from palliative care. Accordingly, strategies for relieving symptoms and improving quality of life are being prioritized over interventions that aim for medium- and long-term outcomes. For a subgroup of patients with advanced HF receiving palliative care, home therapy with continuous inotropes may be considered and integrated into general palliative care.

Case report

A 77-year-old male patient was being followed up at the Hospital de Clínicas, Porto Alegre, Rio Grande do Sul, Brazil for long-standing severe HF with reduced ejection fraction with ischemic etiology. In spite of interventional therapy with angioplasty, optimized treatment with medications for HF, and electrical devices, he evolved with disease progression, cachexia, and frequent readmissions. The patient had a prohibitive risk for heart transplantation due to age, severe malnutrition, and renal failure. During one of the hospitalizations, he evolved with intravenous inotropic dependence to control symptoms at rest. Several attempts to gradually withdraw the inotropic medication were unsuccessful, due to recurrence of dyspnea, fatigue, symptomatic hypotension, and other symptoms associated with low cardiac output and pulmonary congestion.

In joint evaluation, the multidisciplinary teams specializing in advanced HF, transplantation, and palliative care at the hospital established, together with the patient, palliative care objectives and measures that prioritized improved quality of life. The doctor of the palliative care team prepared, together with the patient, the advance directives of will, which were attached to the medical record. In order to better control symptoms and promote dehospitalization, the possibility of home use of continuous intravenous inotrope was discussed. The patient and the family, being aware of the potential risks and benefits, agreed to use of the medication, and approval was obtained from the Regional Councils of Medicine and Nursing. A protocol was organized in conjunction with the Home Care Program (HCP) of the Conceição Hospital Group, which is linked to the Municipal Health Department of Porto Alegre, so that the patient could be followed up through home visits within the Brazilian Unified Health System (SUS, abbreviation in Portuguese). The inotropic medication was funded and provided by the HCP on an exceptional basis. Guidelines were provided on the use of the drug and the infusion pump, disease progression, symptom control, and emergency situations. Nursing, pharmacy, nutrition, physiotherapy, psychology, and social work teams participated in the planning of dehospitalization with inotropes (Figure 1).

The patient was discharged with a continuous infusion of milrinone 0.27 mcg/kg/min, and he remained at home for approximately 20 days, followed up with home visits by the teams from the HCP and the original hospital. No complications were registered, and the patient, even though he was faced with limitations, remained comfortable and was able to perform activities that gave him pleasure, such as sitting on the veranda, being close to friends from his neighborhood and his routine, and the daily affection of his children. The family, who participated in the entire construction of care, showed high satisfaction with the home treatment. After this period, the patient was readmitted due to HF progression, and he died during hospitalization.

Discussion

This case report describes the implementation of home use of an intravenous inotrope as a strategy to improve the quality of life of a patient with advanced HF in palliative care within the SUS. This is considered a pioneering initiative in Brazil, and there are no other reports in the context of Brazil.

The prevalence of HF and advances in HF therapy have increased the proportion of patients living with the disease and its long-term consequences. Accordingly, the proportion of patients with advanced stage disease who require palliative care is also increasing.[1] This change in the epidemiology of HF

Keywords

Milrinone. Dobutamine. Palliative Care. Heart Failure. Home Care Services.

Mailing Address: Ana Paula Chedid Mendes •
Hospital Universitário Antônio Pedro, Serviço de Cardiologia – Rua Marquês de Paraná, 303. Postal Code 24033-900, Niterói, RJ – Brazil
E-mail: anapchedid@gmail.com
Manuscript received March 14, 2022, revised mansucript March 17, 2022, accepted March 17, 2022

DOI: https://doi.org/10.36660/abchf.20220024

Figure 1 – *Training of the Home Care Program Team of the Conceição Hospital Group for home use of inotropic medications in patients with advanced heart failure, held in July 2017.*

is accompanied by an increase in the home use of inotropic medications in developed countries, as a bridge to advanced therapy (heart transplantation and mechanical circulatory assist devices) or as an integrated strategy for palliative care. Between 2010 and 2014, there was a 63% and 44% increase in the number of Medicare beneficiaries in the United States who received milrinone or dobutamine, respectively, for home use.[2] Although, in Brazil, there are still many limitations (economic, social, structural, and legal) to hospital discharge with continuous inotropic infusion, we have reported a successful case of home use of continuous inotrope within the SUS, with the objective of dehospitalization, symptom relief, and improved quality of life in a patient with terminal HF receiving palliative care.

In 2021, updates to the Brazilian HF Guidelines recommended continuous intravenous inotropic outpatient therapy as a palliative treatment for symptom control in patients with advanced HF who were not eligible for mechanical circulatory assist devices or heart transplantation (class IIb).[3] The selection of patients who will potentially benefit from palliative inotropic use is based on clinical, social, and economic aspects.[4] Table 1 proposes the main aspects for evaluation and planning of home use of continuous intravenous inotrope. The use of these medications in the home environment should be considered for patients who, after starting the inotrope while still in a hospital environment, demonstrate hemodynamic and symptomatic improvement, with failed attempts to suspend the inotrope. On the other hand, their use is contraindicated in the presence of uncontrollable and refractory arrhythmias. The benefits and complications must be discussed with patients and their families. The initiation of continuous inotropic therapy at home must be in accordance with the patient's wishes and goals, and the hospital discharge plan must involve a multidisciplinary team and professionals with experience in palliative care, in addition to ensuring training and education for patients, family members, and caregivers. The structure of the patient's home must be evaluated in terms of the electricity network, telephone access, and proximity to a healthcare team.

Regardless of the main indication of bridge to transplantation/mechanical support or palliation, the majority of studies have shown an improvement in New York Heart Association functional class with outpatient inotrope use.[4] A study published in 2020[5] revealed 50% mortality at 1 year in patients in palliative care using dobutamine at home, which represented a slightly better result than in previously published series.[6,7] Arrhythmias, infections, and hospitalizations are the most frequent complications during home inotropic therapy. In a cohort of 197 patients using inotropes at home,[8] 17% had 1 or more implantable cardioverter-defibrillator shocks, 82% being appropriate shocks. The risk of shock was not associated with the dose of the inotrope, and 29% of patients had 1 or more infections during follow-up, bacteremia being the most common type of infection. Furthermore, 57% had 1 or more hospitalizations, and the most common causes of hospitalizations were worsening HF symptoms (41%), infections (20%), and arrhythmias (12%).

In spite of the possible complications, improved functional class and symptom control are fundamental points to consider in relation to treatment. Furthermore, practices in follow-up care can minimize complications. Mortality is tending to decrease, and this may be related to the use of lower doses of inotropes in more recent studies. Therefore, it is necessary to endeavor to discharge from the hospital with the minimum dose necessary to control symptoms and improve hemodynamics; to ensure regular follow-up with the multidisciplinary palliative care and HF teams; to control risk factors for arrhythmia, for example, by monitoring electrolytes and considering starting amiodarone, as suggested in some international study protocols; and, finally, to be aware of diminished inotropic response over time due to tachyphylaxis and to consider dose titration according to symptoms and change in clinical condition.

In Brazil, intravenous inotropic medication for home use is not provided by the public network. In this case report, the medication was supplied by the Conceição Hospital Group, which has a HCP linked to the Municipal Health Department of Porto Alegre. In a retrospective study,[5] cost analysis of home use of dobutamine in patients with advanced HF in palliative care indicated a significant cost reduction at 3, 6, and 12 months, mainly due to the decrease in hospitalizations for HF. In addition to the daily cost of the medication, the following were analyzed: hospitalization for HF, venous catheter insertion, costs related to catheter replacement, use of thrombolytics to clear the catheter, and costs of home nursing.

The international literature has demonstrated favorable results for the use of home inotropic therapy, with improved functional status and reduced hospitalizations for HF. In economic terms, home use of dobutamine is associated with

Table 1 – Recommendations for evaluation and planning of home use of continuous intravenous inotrope

- Appropriate indication and exhaustion of other therapeutic possibilities
- Biopsychosocial assessment of the patient (living conditions, self-care capacity, presence of a caregiver)
- Patient and caregiver are aware of the risks and benefits of the medication, and they agree with the therapy
- Discussion of patient's preferences and values, with establishment of advance directives of will
- Verification of the ethical and legal aspects particular to each region
- Clinical stability in inotropic use, initiated in the in-hospital context
- Availability of the inotropic medication and an infusion pump
- Appropriate venous access, preferably peripherally inserted central catheter
- Home care service for patient evaluation and exchange of drug infusions
- Detailed and express guidance on use of the medication (dilution, dose adjustment, compatibilities, and stability) and its adverse effects
- Guidance on how to proceed in the event of complications (contact telephone numbers, reference emergency service, possibility of replacement in case of lack of medication, electricity network for the infusion pump to work)

significant cost savings. Regarding milrinone, as it exceeds the cost of dobutamine in the United States, a study from the United States showed that there was no cost reduction after 6 months due to the cumulative costs of the medication.[7] Brazilian studies could assist in its incorporation by the SUS.

Conclusion

The number of patients with advanced HF is increasing, and an elevated proportion of these patients will not be candidates for advanced therapies. Treatment strategies should be encouraged and systematically organized to ensure comfort and quality of life for these patients. We have described a case where, aiming to humanize care in the terminal stage, home use of continuous intravenous inotrope allowed hospital discharge, control of HF symptoms, and comfort for the patient together with his family members in the home environment.

Author Contributions

Conception and design of the research: Mendes APC, Zambonato R, Hastenteufel LCT, Orlandin L, Clausell N, Goldraich LA; Writing of the manuscript: Mendes APC, Hastenteufel LCT; Critical revision of the manuscript for intellectual contente: Mendes APC, Zambonato R, Hastenteufel LCT, Clausell N, Goldraich LA.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Truby LK, Rogers JG. Advanced Heart Failure: Epidemiology, Diagnosis, and Therapeutic Approaches. JACC Heart Fail. 2020;8(7):523-6. doi: 10.1016/j.jchf.2020.01.014.
2. Gilstrap LG, DeFilippis EM, Stevenson LW. An Unintended Consequence of the 21st-Century Cures Act for Patients With Heart Failure. Circulation. 2017;136(2):123-5. doi: 10.1161/CIRCULATIONAHA.117.028747.
3. Marcondes-Braga FG, Moura LAZ, Issa VS, Vieira JL, Rohde LE, Simões MV, et al. Emerging Topics Update of the Brazilian Heart Failure Guideline - 2021. Arq Bras Cardiol. 2021;116(6):1174-212. doi: 10.36660/abc.20210367.
4. Chuzi S, Allen LA, Dunlay SM, Warraich HJ. Palliative Inotrope Therapy: A Narrative Review. JAMA Cardiol. 2019;4(8):815-22. doi: 10.1001/jamacardio.2019.2081.
5. Martens P, Vercammen J, Ceyssens W, Jacobs L, Luwel E, van Aerde H, et al. Effects of intravenous home dobutamine in palliative end-stage heart failure on quality of life, heart failure hospitalization, and cost expenditure. ESC Heart Fail. 2018;5(4):562-9. doi: 10.1002/ehf2.12248.
6. Hashim T, Sanam K, Revilla-Martinez M, Morgan CJ, Tallaj JA, Pamboukian SV, et al. Clinical Characteristics and Outcomes of Intravenous Inotropic Therapy in Advanced Heart Failure. Circ Heart Fail. 2015;8(5):880-6. doi: 10.1161/CIRCHEARTFAILURE.114.001778.
7. Hauptman PJ, Mikolajczak P, George A, Mohr CJ, Hoover R, Swindle J, et al. Chronic Inotropic Therapy in End-Stage Heart Failure. Am Heart J. 2006;152(6):1096.e1-8. doi: 10.1016/j.ahj.2006.08.003.
8. Acharya D, Sanam K, Revilla-Martinez M, Hashim T, Morgan CJ, Pamboukian SV, et al. Infections, Arrhythmias, and Hospitalizations on Home Intravenous Inotropic Therapy. Am J Cardiol. 2016;117(6):952-6. doi: 10.1016/j.amjcard.2015.12.030.