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

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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.

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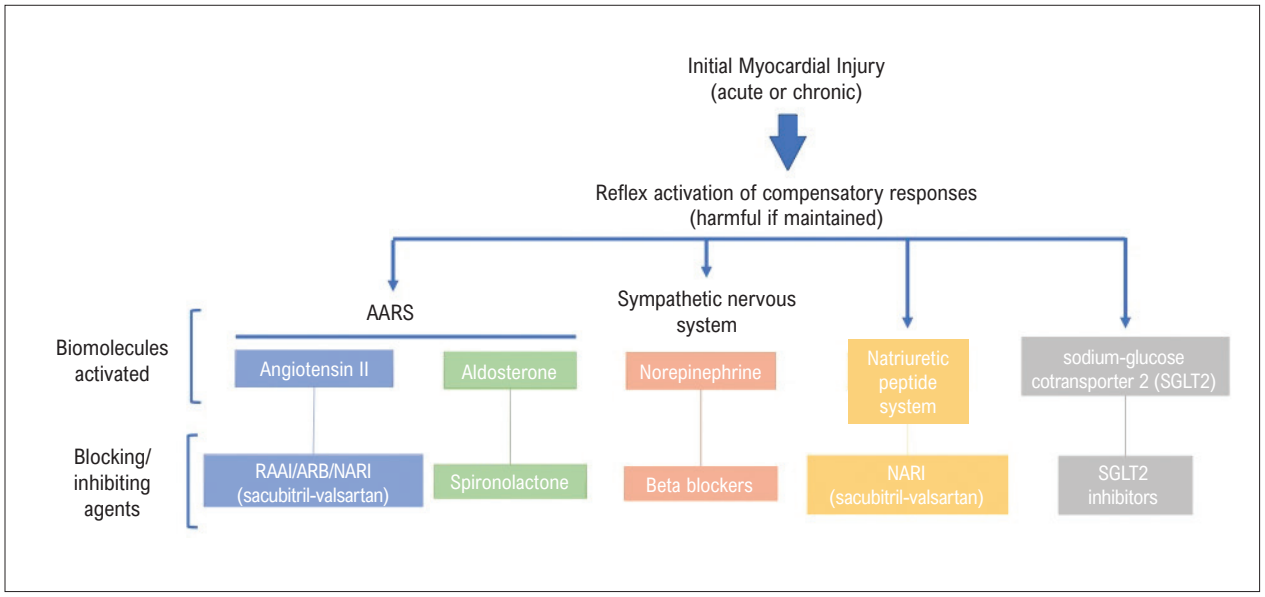

Figure 1 – *The pillars of treatment for HFREF.*

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.

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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.

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