

Pharmacological Treatment Sequencing for Heart Failure with Reduced Ejection Fraction

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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) \leq 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.

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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, SGLT2i 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),

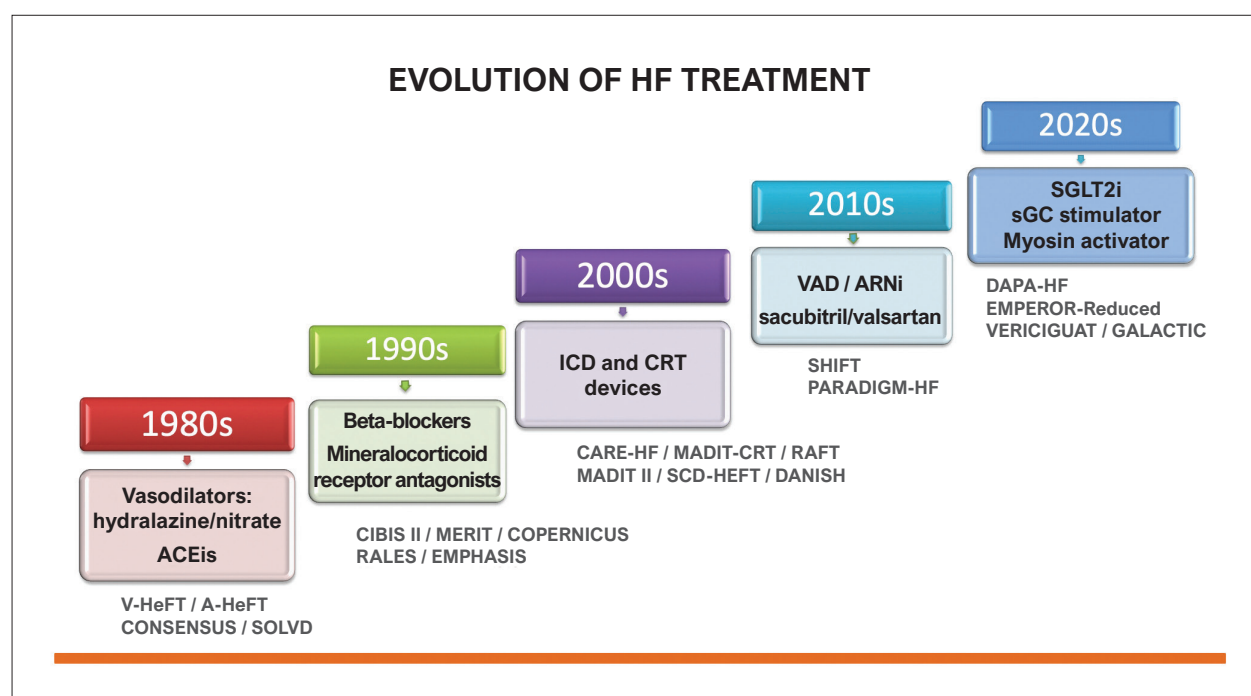


Figure 1 – Evolution of the treatment of heart failure (HF) with reduced ejection fraction. ACEi: angiotensin-converting enzyme inhibitor; ICD: implantable cardioverter-defibrillator; CRT: cardiac resynchronization therapy; VAD: long-term ventricular assist device; ARNi: angiotensin receptor-neprilysin 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 recommendation. 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, pharmacological 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.

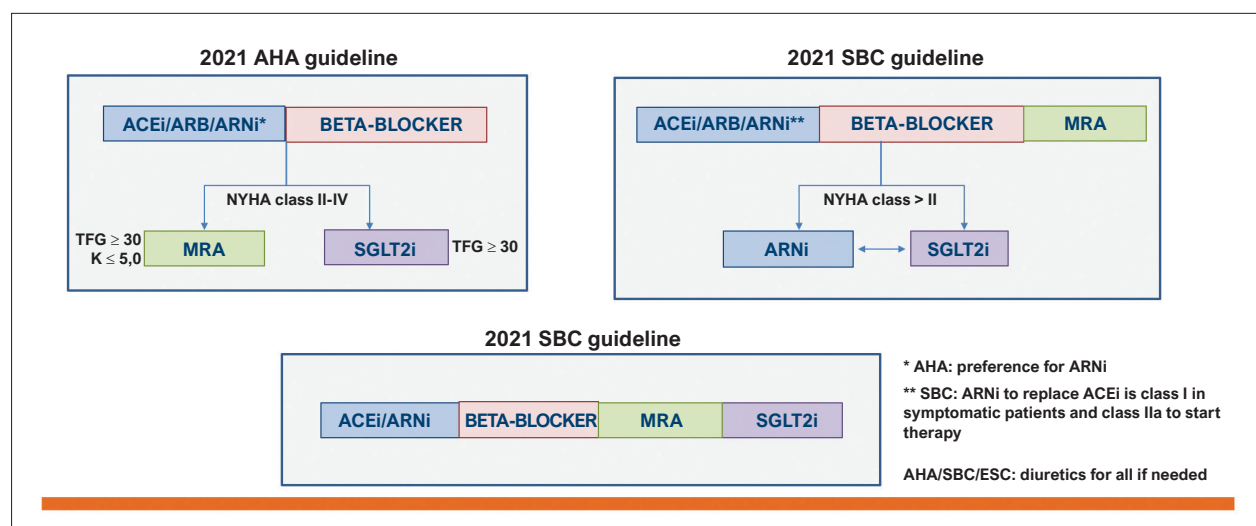


Figure 2 – Use of first-line treatment of HFrEF according to different guidelines. AHA: American Heart Association; SBC: Brazilian Society of Cardiology; ESC: European Society of Cardiology; ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; ALDO ANT: aldosterone antagonist;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

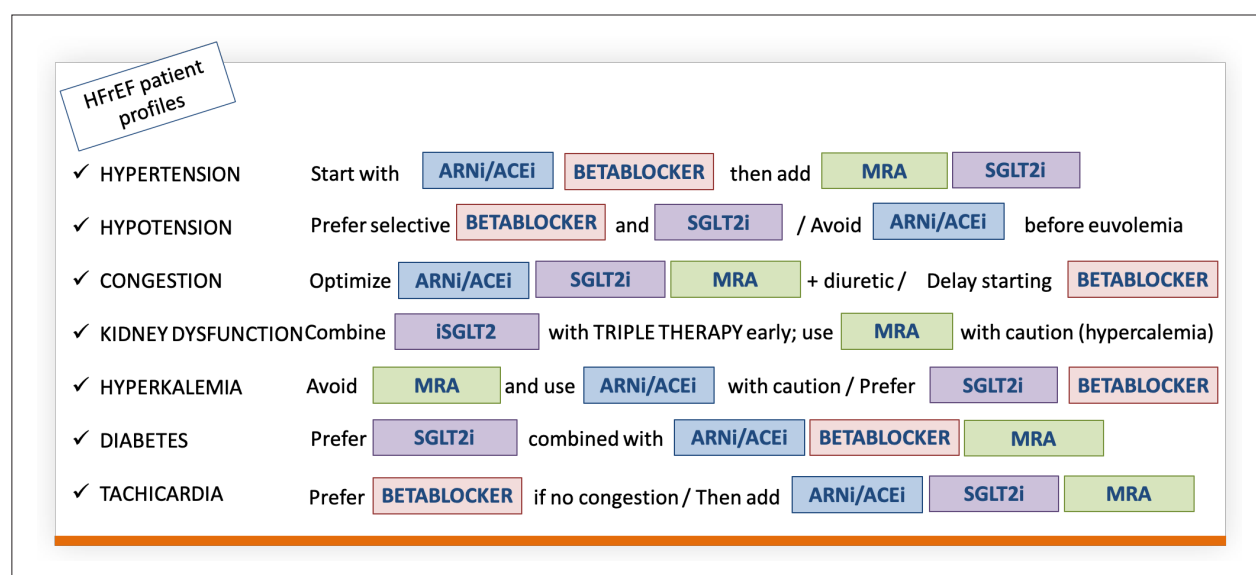


Figure 3 – A proposal of clinical management of patients with HFrEF according to individual characteristics. HFrEF: heart failure with reduced ejection fraction; ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; MRA: mineralocorticoid receptor antagonist; SGLT2i: sodium-glucose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

Potential Conflict of Interest

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

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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.

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