

HFREF Pharmacological Treatment Sequencing: The Traditional Approach

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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.

Keywords

Medication Therapy Management, Heart Failure, Ventricular Ejection Fraction

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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 strategy¹² 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.

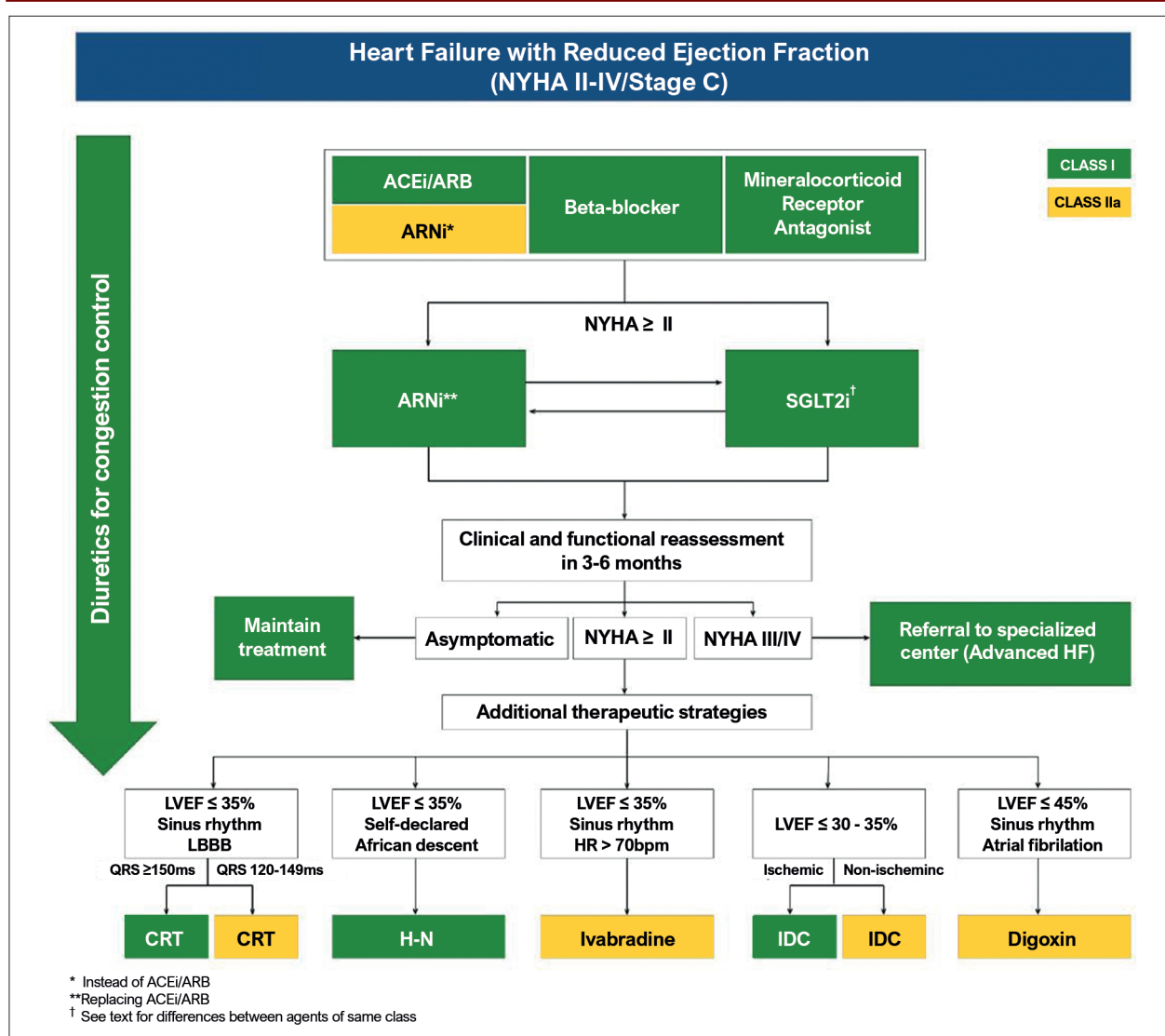


Figure 1 – Treatment algorithm for heart failure with reduced ejection fraction. ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; ARNi: angiotensin receptor-neprilysin inhibitor; CRT: cardiac resynchronization therapy; HF: heart failure; H-N: hydralazine-nitrate; HR: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

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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.

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Study Association

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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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