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

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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

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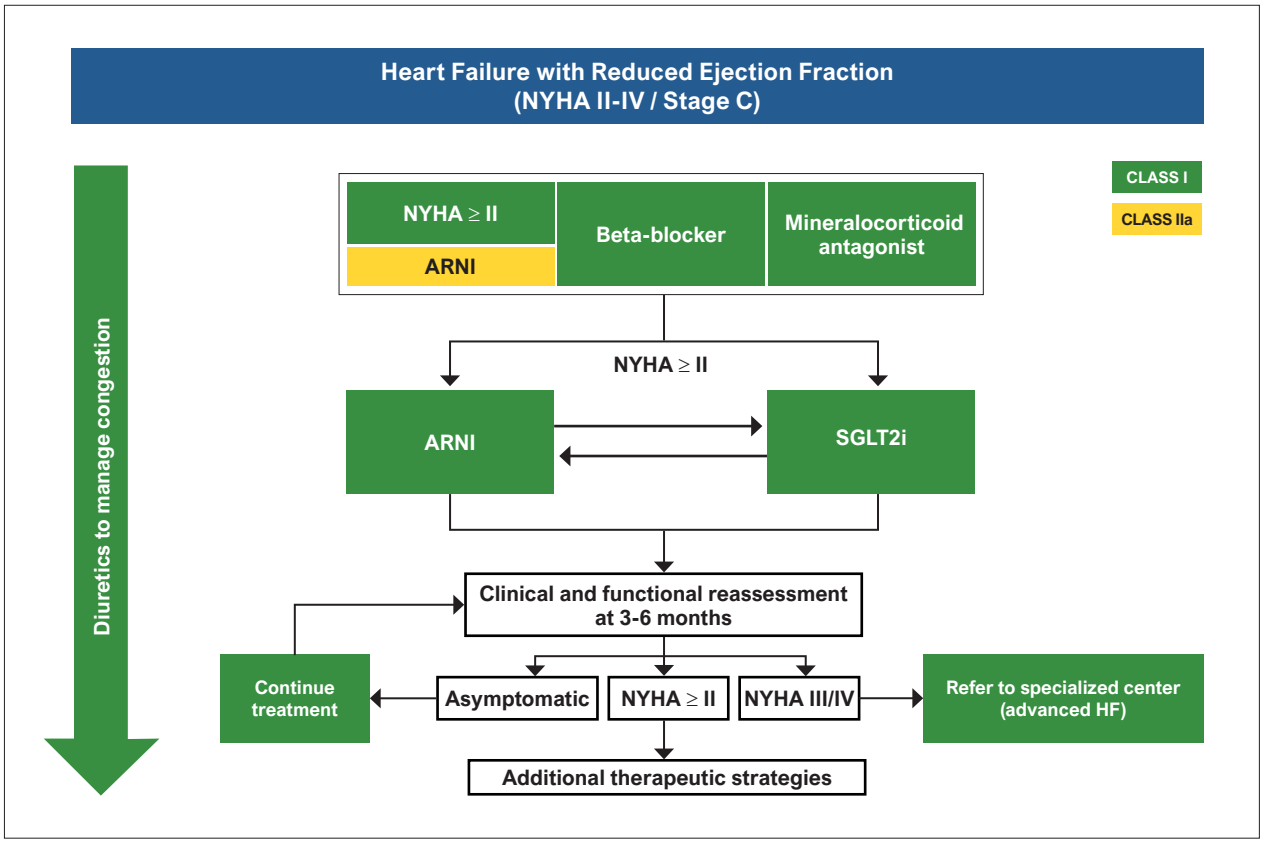

Figure 1 – *Algorithm for pharmacological treatment of heart failure with reduced ejection fraction adapted from the Brazilian Society of Cardiology. ARB: angiotensin receptor blocker; ACEi: angiotensin-converting enzyme inhibitor; ARNI: angiotensin receptor-neprilysin inhibitor; SGLT2i: sodium-glucose 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.

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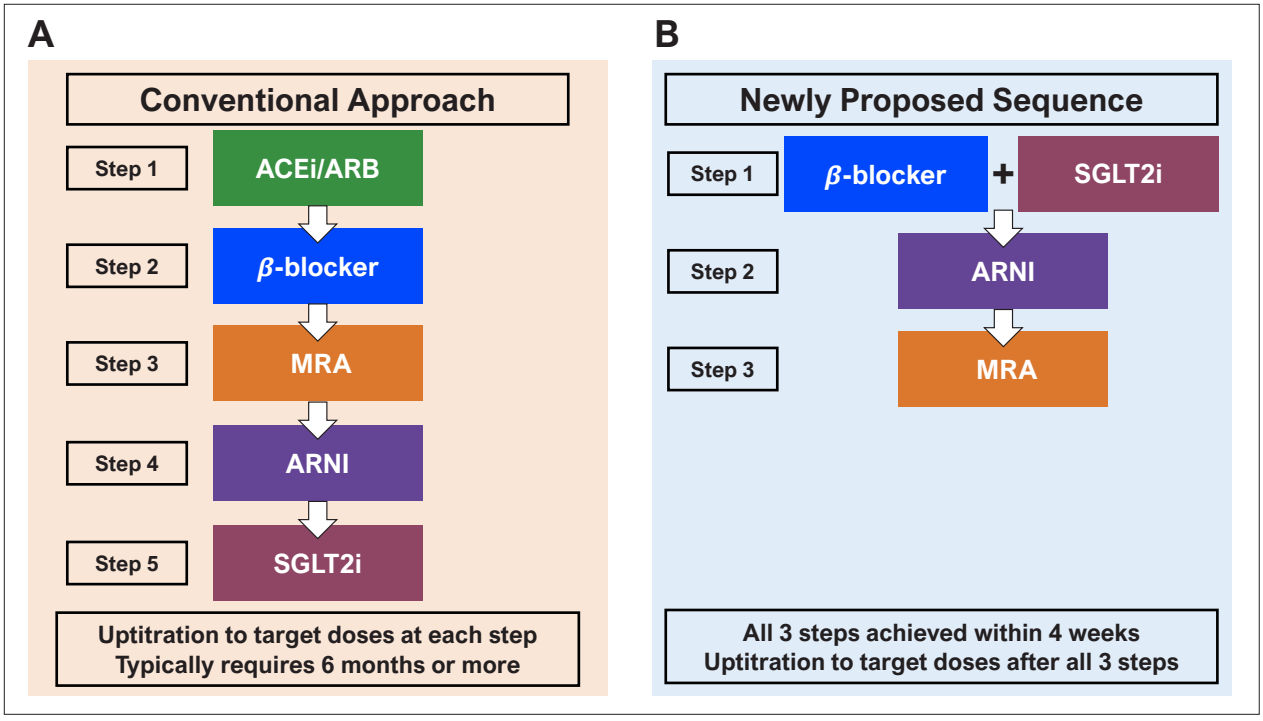

Figure 2 – *Conventional approach and rapid sequencing approach proposed by McMurray and Packer for the initiation of foundational drugs in outpatients with heart failure with reduced ejection fraction. MRA: mineralocorticoid receptor antagonist; ARB: angiotensin receptor blocker; ACEi: angiotensin-converting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

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