Circulation

PERSPECTIVE

# How Should We Sequence the Treatments for Heart Failure and a Reduced Ejection Fraction?

## A Redefinition of Evidence-Based Medicine

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Large-scale trials have demonstrated the efficacy of sacubitril/valsartan, β-blockers, mineralocorticoid receptor antagonists (MRAs), and sodium-glucose cotransporter 2 inhibitors (SGLT2is) as disease-modifying agents that (when combined) represent foundational therapy for heart failure and a reduced ejection fraction (HFrEF). The conventional approach to achieving treatment with all 4 drug classes is to prescribe them in the precise sequence in which they were tested in clinical trials over the past 40 years. Physicians are asked to start with angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, to be followed by a β-blocker, then an MRA, then a neprilysin inhibitor, and, finally, a SGLT2i. Prescribers are advised to titrate the dose of each drug class to the target dose used in large-scale trials before initiating the next recommended drug class. This approach recapitulates the sequence by which these agents were developed for the treatment of heart failure.

The current approach suffers from many important limitations. First, it assumes that our most effective and well-tolerated treatments were developed first. However, historical precedent is not a strong rationale for making therapeutic recommendations; digitalis has been used for >200 years but is no longer a cornerstone of therapy. Second, it assumes that foundational treatments are effective only when titrated to target doses. Yet, low doses of drugs for HFrEF yield important benefits to reduce morbidity and mortality, and target doses are often only modestly more effective than low starting doses in reducing the risk of cardiovascular death.[1] Third, it assumes that the efficacy and safety of each drug class were tested in clinical trials that required patients to be receiving all background therapy at target doses. However, in these trials, most patients were receiving subtarget doses of recommended treatments, and even in the most recently completed trials a meaningful proportion was not treated with an MRA or an angiotensin receptor neprilysin inhibitor at any dose.

The current approach to the sequencing of drug treatments has had adverse consequences on the adoption of disease-modifying therapies for HFrEF. If physicians prioritize the achievement of target doses of each drug class before initiating treatment with the next, it may take ≥6 months to prescribe all recommended treatments. This estimate assumes that physicians and patients are fully dedicated to potentially adjusting treatment regimens at most visits. Such conditions are rarely met in clinical practice, explaining why only a small proportion of patients with HFrEF are receiving all recommended drug classes at target doses. More importantly, even if the current guideline-recommended approach was fully adopted, a delay of 6 months is unacceptable, because each of the foundational drugs has been shown to reduce morbidity and mortality within 30 days of initiating treatment.[2] With every passing visit, the absence of ≥1 therapy results in unnecessary hospitalizations and deaths.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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## PROPOSAL OF A NEW ALGORITHM FOR SEQUENCING OF FOUNDATIONAL TREATMENTS

Any new algorithm for the sequencing of foundational treatments can be based on several principles. First, the magnitude of the treatment benefit of each drug class is independent of that produced by other agents. Specifically, the use of MRAs does not modify the efficacy of an angiotensin receptor neprilysin inhibitor, and the use of sacubitril/valsartan does not influence the efficacy of an SGLT2i. Second, low starting doses of foundational drugs are effective in reducing morbidity and mortality. Low doses of enalapril, carvedilol, and eplerenone exert meaningful effects on the risk of death or hospitalization for heart failure, as evidenced by the benefits seen in large-scale trials before protocol-mandated increments in dose.[2–4] For SGLT2i, the starting dose is identical to the target dose. Third, the addition of a new drug class yields benefits that are greater in magnitude than up-titration of existing drug classes. Indeed, 3- to 7-fold increments in the dose of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker produces none of the mortality reduction seen with the addition of a β-blocker, neprilysin inhibitor, or SGLT2i.[1] Fourth, the proper sequencing of drug classes can improve safety and tolerability. Specifically, neprilysin inhibition can reduce the risk of renal insufficiency produced by an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and both neprilysin inhibitors and SGLT2 inhibitors can minimize the risk of hyperkalemia with the use of MRAs.[5] Fifth, and importantly, because much of the benefits of foundational treatments are seen within 30 days of initiating treatment, the algorithm should achieve therapy with all 4 classes of drugs within 4 weeks.

Our proposed "new sequence" algorithm (Figure) involves 3 steps, to be initiated in a patient in whom diuretics has achieved clinical euvolemia.

Step 1 is simultaneous initiation of treatment with a β-blocker and an SGLT2i. β-Blockers are (arguably) our single most effective drug class for the treatment of HFrEF, particularly with respect to the reduction of sudden death. SGLT2is have a striking effect to reduce the risk of hospitalizations for heart failure, and this benefit (potentially acting in concert with their early diuretic action) may mitigate the short-term risk of worsening heart failure that may occur after a β-blocker is started.

Step 2 is addition of sacubitril/valsartan, within 1 to 2 weeks of step 1. If the patient's systolic blood pressure is <100 mm Hg, it may be prudent to first evaluate tolerance, in relation to hypotension, with an angiotensin receptor blocker before switching to an angiotensin receptor neprilysin inhibitor. Any hypotensive effects commonly resolve with repeated dosing or with adjustment of the dose of concurrently administered diuretics.

Step 3 is the addition of an MRA, within 1 to 2 weeks of step 2, if serum potassium is normal and renal function is not severely impaired. The favorable effects of

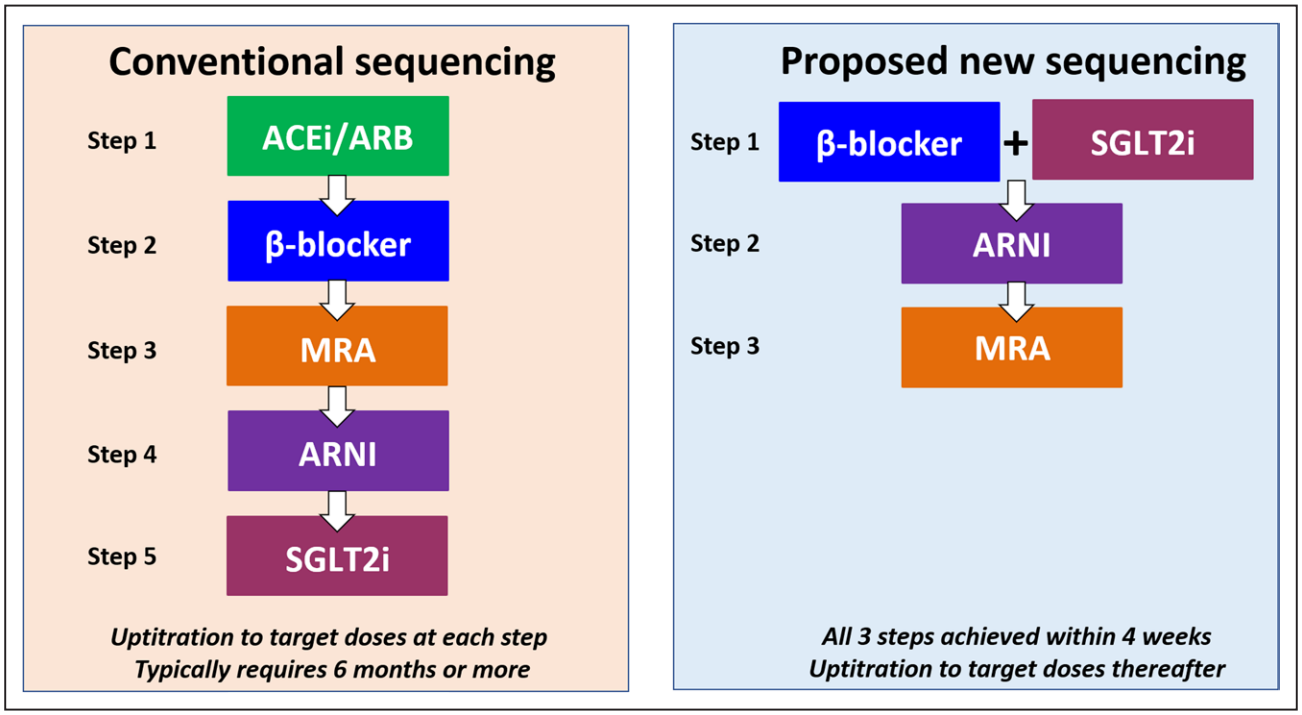


**Figure. Conventional and novel sequencing strategies for the implementation of foundational treatments in ambulatory patients with heart failure and a reduced ejection fraction.**

ACE indicates angiotensin-converting enzyme; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin recpetor neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; and SGLT2, sodium-glucose cotransporter 2.

neprilysin inhibitors and SGLT2i to improve renal function and potassium homeostasis may increase the tolerability of MRAs. MRAs may be step 2 in a patient with troublesome hypotension.

The proposed algorithm represents one possibility of many and can be individualized to specific circumstances. It is most appropriate for outpatients, and more caution is required in patients hospitalized for decompensated heart failure. β-Blocker therapy should only be initiated in the hospital after intravenous therapy has been discontinued for several days and the patient is clinically euvolemic, defined as the absence of rales and ascites and the presence of no more than minimal peripheral edema.

Used in appropriate patients, the approach outlined achieves treatment with all 4 foundational treatments within 4 weeks. Up-titration to target doses should be pursued thereafter. This sequencing maximizes the likelihood that highly effective therapies will be implemented in a manner that rapidly prevents deaths and hospitalizations and enhances the tolerability of concurrently or subsequently administered treatments.

## ARTICLE INFORMATION

The podcast and transcript are available as a Data Supplement at https://www.ahajournals.org/doi/suppl/10.1161/CIRCULATIONAHA.120.052926.

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