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.

Key Words: adrenergic beta-antagonists ■ aldosterone ■ angiotensin converting enzyme inhibitors ■ heart failure ■ neprilysin ■ receptors, mineralocorticoid ■ sodium-glucose transport proteins

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