VIEWPOINT

Simultaneous or Rapid Initiation of Combination Therapy for Heart Failure With Preserved Ejection Fraction

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After decades of neutral clinical trials, there have been multiple recent major advancements in medical therapy for patients with heart failure (HF) with mildly reduced ejection fraction (HFmrEF) or preserved ejection fraction (HFpEF).[1-4] The ability to modify the natural history of HF in patients with EF greater than 40% with medications should prompt a fundamental shift in how we implement therapy in clinical practice. Herein, we propose a multidrug approach to treatment for HFmrEF and HFpEF and present the case for simultaneous or rapid sequence initiation of combination therapy.

3 Pillars of Medical Therapy

Three classes of therapy have demonstrated definitive clinical benefits for HFmrEF and HFpEF (**Figure**). In large clinical outcome trials, sodium-glucose cotransporter inhibitors (SGLTis) and a nonsteroidal mineralocorticoid receptor antagonist (nsMRA), finerenone, have each been shown to reduce the relative risk of cardiovascular (CV) death or HF hospitalization by 20% and 16%, respectively.[1,3] Additionally, each therapy significantly improved patient-reported health status. For both medications, efficacy was consistent across prespecified demographic and clinical subgroups, supporting broad application.[1,3]

Most US patients with HFmrEF or HFpEF are overweight or obese. Among patients with HFpEF and obesity, treatment with the combined glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist (GLP-1RA) tirzepatide significantly reduced the risk of CV death or worsening HF.[4] Additionally, 3 trials for HFmrEF or HFpEF have shown that GLP-1RA therapy significantly improves patient symptoms and physical limitations while simultaneously facilitating weight loss.[2,4]

Rationale for Rapid Initiation of Combination Medical Therapy

Early and Additive Clinical Benefits Following Initiation

Clinical trials of SGLTis and finerenone yielded early separation of event curves within days to weeks of initiation.[1,5] Barring absolute contraindications, delaying initiation of either therapy, even for a few weeks, might equate with exposure to excess clinical risk.

Noting that SGLTi was the first foundational medical therapy for HF with EF greater than 40%, some may question whether additional therapies are incremental. Limited but suggestive data indicate the absence of attenuation of treatment effect regardless of background therapy with SGLTi, nsMRA, and/or GIP and GLP-1RA for patients with HFmrEF or HFpEF.[1-4] For example, in the FINEARTS-HF trial of finerenone, among 817 participants (14%) receiving an SGLTi at baseline, the relative benefits of finerenone on CV death or worsening HF were consistent with those of patients without an SGLTi at

Figure. Suggested Simultaneous or Rapid Sequence Initiation of Combination Medical Therapy for Heart Failure (HF) With Mildly Reduced Ejection Fraction (HFmrEF) or Preserved Ejection Fraction (HFpEF)

Therapy	Day 1	Week 4	Week 8	Week 12	Week 16	Clinical benefits
SGLTi	Initiate					20% RRR for CV death or HF hospitalization Improvement in patient-reported health status (mean 1- to 6-point improvement in KCCQ)
nsMRA[a]	Initiate	Titrate, as tolerated				16% RRR for CV death or worsening HF Improvement in patient-reported health status (mean 1.6-point improvement in KCCQ-TSS)
GLP-1RA (obesity)	Initiate	Titrate, as tolerated	Titrate, as tolerated	Titrate, as tolerated	Titrate, as tolerated	38% RRR for CV death or worsening HF Improvement in patient-reported health status (mean 6- to 8-point improvement in KCCQ-CSS)
ARNI, (EF <55%-60%)[b]	Initiate	Titrate, as tolerated	Titrate, as tolerated			Potential 22% RRR for total HF hospitalization or CV death
Steroidal MRA[a] (nsMRA not feasible)	Initiate	Titrate, as tolerated				Potential 18% RRR for CV death, aborted cardiac arrest, and HF hospitalization among individuals in the Americas
β-Blocker (EF 41%-49%)[c]	Initiate	Titrate, as tolerated	Titrate, as tolerated	Titrate, as tolerated		Potential CV death benefit for patients in sinus rhythm

CV indicates cardiovascular; GLP-1RA, glucagon-like peptide-1 receptor agonist; KCCQ, Kansas City Cardiomyopathy Questionnaire; RRR, resistive reserve ratio; SGLTi, sodium-glucose cotransporter inhibitors.

[a]For nonsteroidal mineralocorticoid receptor antagonist (nsMRA) and steroidal MRA, close laboratory monitoring of serum potassium is required. Assessment of tolerability includes monitoring for hyperkalemia.

[b]For angiotensin receptor-neprilysin inhibitor (ARNI)–eligible individuals where ARNI therapy is not feasible, treatment with an angiotensin II receptor blocker therapy can be considered. ARNI may be titrated more frequently than every 4 weeks, as tolerated

[c]β-blocker may be titrated more frequently than every 4 weeks, as tolerated.

baseline. Likewise, in the SUMMIT trial of tirzepatide, 256 participants (35%) were treated with an MRA at baseline, with consistent relative risk reduction with tirzepatide regardless of MRA use.[4]

Early Consideration of Additional Therapies for Select Patients

To further reduce residual clinical risk, based on subgroup analyses of randomized trials, additional guideline-recommended therapies may be considered for select patients. Such therapies include angiotensin receptor-neprilysin inhibitor (ARNI) for patients with EF below normal, steroidal MRA if nsMRA is not feasible, and β-blocker for HFmrEF. It is notable that most patients with HF and EF greater than 40% are either already receiving a β-blocker and/or renin-angiotensin-aldosterone system inhibitor (RAASi) at the time of HF diagnosis or have comorbidities where such therapies are strongly recommended (eg, RAASi for chronic kidney disease).

Addressing Hesitation With Rapid Initiation of Combination Therapy

Some may question whether rapidly initiating SGLTi, nsMRA, and GLP-1RA may increase risk of medication intolerance. Moreover, there are few data assessing concurrent administration of all 3 drug classes for HFmrEF or HFpEF. However, it is conceivable that simultaneous or rapid initiation could improve tolerability across these 3 medication classes. For example, SGLTis curb rates of hyperkalemia and have been shown to reduce discontinuation of steroidal MRA. Improved health status with 1 therapy may assist tolerability of other therapies. While select adverse effects may occur, each of the 3 individual classes of medications have rates of total adverse events similar to or lower than placebo in randomized trials.[1-4] Nonetheless, for nsMRA or steroidal MRA, close laboratory monitoring of serum potassium is required.

Despite this evidence, hesitancy may remain for rapid initiation of combination disease-modifying therapy since there are no dedicated randomized clinical trials of this specific approach with SGLTis, nsMRA, and GIP or GLP-1RAs. Such trials are warranted and prospective pragmatic trials may be considered.

All 3 core medications, as well as the selective use of ARNI, are branded medications that may not be currently affordable or accessible for all patients. Importantly, out-of-pocket costs remain a barrier for some patients. However, starting in January 2025, out-of-pocket cost for medications are planned to be capped at $2000 per year for patients with Medicare Part D plans. Continued efforts are needed to best ensure equitable access to these expensive medications.

Rapid Initiation of Combination Therapy vs the Status Quo

In US clinical practice, within 1 year of discharge from a hospitalization for HF with EF greater than 40%, more than 1 in 4 patients are dead, approximately 3 in 10 are readmitted for HF, and more than 1 in 2 are readmitted for any reason.[6] These event rates occur in the context of the status quo approach, with slow, selective, and stepwise introduction of medical therapies, if they are introduced at all. Event rates are high, and so too are the potential risks of omitting or delaying therapies with potentially early and additive clinical benefits.

We believe that the totality of evidence available today suggests that the potential clinical benefits of simultaneous or rapid initiation outweigh the potential risks, especially compared with the status quo approach of gradual medication optimization. As the HF community adjusts to the reality of 3 definitively proven classes of medications for patients with HFmrEF and HFpEF, we believe the discussion should not be over which class of medication to pick. Rather, we believe the optimal strategy is one of simultaneous or rapid sequence initiation of combination therapy with SGLTi, nsMRA, and GIP or GLP-1RA (if comorbid obesity) to all eligible patients, without delay.

ARTICLE INFORMATION

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