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EDITORIAL

Beyond trial neutrality: treatment discontinuation and the hidden signal in SPIRIT-HF trial

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Abstract

Taken together, the findings from SPIRIT-HF challenge a simplistic interpretation of neutral trial results from an under-powered study, and instead appear to highlight the critical role of treatment durability in determining clinical outcomes in heart failure with preserved ejection fraction and heart failure with mildly reduced ejection fraction, where patients are older, multi-morbid, and physiologically vulnerable, the balance between efficacy and tolerability is particularly fragile. Importantly, treatment discontinuation should not be viewed merely as an adverse event, but as a clinically meaningful signal reflecting both patient vulnerability and potential loss of therapeutic benefit. These observations suggest that the effectiveness of neurohormonal therapies may depend as much on their sustained use as on their intrinsic pharmacologic efficacy. Accordingly, future therapeutic strategies should prioritize not only the initiation of disease-modifying treatments but also their long-term tolerability, adherence, and continuity.

Key words: heart failure with preserved ejection fraction, heart failure with mildly reduced ejection fraction, SPIRonolactone In The Treatment of Heart Failure trial.

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Introduction

Heart failure with preserved/mildly reduced ejection fraction (HFpEF/HFmrEF) represents one of the most rapidly expanding, and therapeutically challenging, domains in cardiovascular medicine.[1,2] In contrast to the substantial therapeutic advances achieved in HFrEF, effective treatments for HFpEF/HFmrEF remain sparse.[1,2] This gap largely reflects the marked heterogeneity of these syndromes and the complex, interrelated pathophysiological mechanisms driven by multiple concomitant comorbidities.[3]

Steroidal mineralocorticoid receptor antagonists w(MRAs) has demonstrated clear morbidity and mortality benefits in HFrEF.[4,5] Similarly aldosterone synthesis inhibitors show promise without definitive evidence of effectiveness yet.[6] However, their role in HFpEF has remained uncertain. This doubt persists in part following the largest trial to date, treatment of preserved cardiac function heart failure with an aldosterone antagonist, which yielded overall neutral results, with signals of benefit confined to select subgroups.[7,8] Interpretation of these findings has been further complicated by regional variability and concerns regarding treatment adherence.[7]

SPIRonolactone in the treatment of heart failure trail

Against this background, the *SPIRonolactone In The Treatment of Heart Failure* (SPIRIT-HF) trial was designed to reconsider the role of spironolactone in a contemporary cohort of patients with symptomatic HFmrEF and HFpEF. It was presented by the studies PI, Professor Frank Edelmann, on 29. March 2026 at the 2026 Congress of the American College of Cardiology in New Orleans.[9-11] The trial focused on clinically meaningful outcomes, including recurrent heart failure (HF) hospitalizations over 24 months and cardiovascular mortality as primary endpoints. Secondary end points included cumulative HF hospitalizations, nonfatal cardiovascular hospitalizations, and all-cause hospitalizations.

In this prospective, multi-center, double-blind, publicly funded trial, 730 participants were randomized in a 1:1 ratio to receive spironolactone or placebo – the original plan was to recruited twice as many patients, but due to lack of funding and problems related to the COVID pandemic the study fell well short of this goal. Eligible patients had symptomatic HF and either

a recent HF hospitalization within the preceding 12 months with elevated natriuretic peptide levels (NT-proBNP >200 pg/mL in sinus rhythm or >600 pg/mL in atrial fibrillation), or elevated natriuretic peptide levels in the absence of recent hospitalization (NT-proBNP >300 pg/mL in sinus rhythm or >900 pg/mL in atrial fibrillation).

Key findings

Although the trial yielded neutral findings with respect to both cardiovascular mortality and HF hospitalizations, with neither outcome reaching statistical significance, a critical aspect of the SPIRIT-HF results lies beyond these primary endpoints, in the temporal pattern of treatment discontinuation and its clinical implications. Although the overall rate ratio for the primary endpoint increased over time at 5 months (p for trend <0.05), this trajectory paralleled a growing burden of adverse events in the spironolactone arm. Rates of hypotension, hyperkalemia, and renal events (all p<0.05), alongside recurrent all-cause hospitalization (p=0.013), were all significantly higher. Importantly, the adverse signals in the spironolactone arm appear to emerge in parallel with increasing rates of drug withdrawal over time, with only approximately half of participants remaining on therapy by 21 months.

These observations introduce two competing considerations, particularly in light of the well-established adverse effect profile of steroidal MRAs. First, tolerability remains a major limitation, especially among complex, multi-morbid patients. Hyperkalemia is the principal dose-limiting toxicity, particularly in those with chronic kidney disease, diabetes, or concomitant renin-angiotensin system inhibition.[4,5,9,10] Even modest elevations in serum potassium frequently lead to dose reduction or discontinuation, interrupting neurohormonal blockade at critical time points.[12-15] Similarly, hypotension, often under-recognized in HFpEF/HFmrEF populations characterized by advanced age and polypharmacy, may further contribute to intolerance and treatment cessation.[12-15] Importantly, these adverse effects do not occur in isolation but reflect a broader renal vulnerability, often signaling impaired renal perfusion and reduced renal reserve, particularly in patients with underlying chronic kidney disease.[15,16]

Second, these findings raise the possibility that the observed safety signal is not solely attributable to spironolactone exposure itself, but rather to the consequences of treatment interruption. In contemporary HF care, discontinuation of disease-modifying therapies, particularly steroidal MRAs, is seldom random and often reflects clinical deterioration, intolerance, or increasing comorbidity burden.[11-14,16] As such, treatment withdrawal may function both as a marker of higher-risk patients and as a mediator of adverse outcomes, amplifying vulnerability in an already fragile population.[15,16] Importantly, the clinical trajectory following discontinuation may be critical, reflecting both loss of therapeutic effect and the underlying instability that necessitated withdrawal (Figure 1).[17-20]

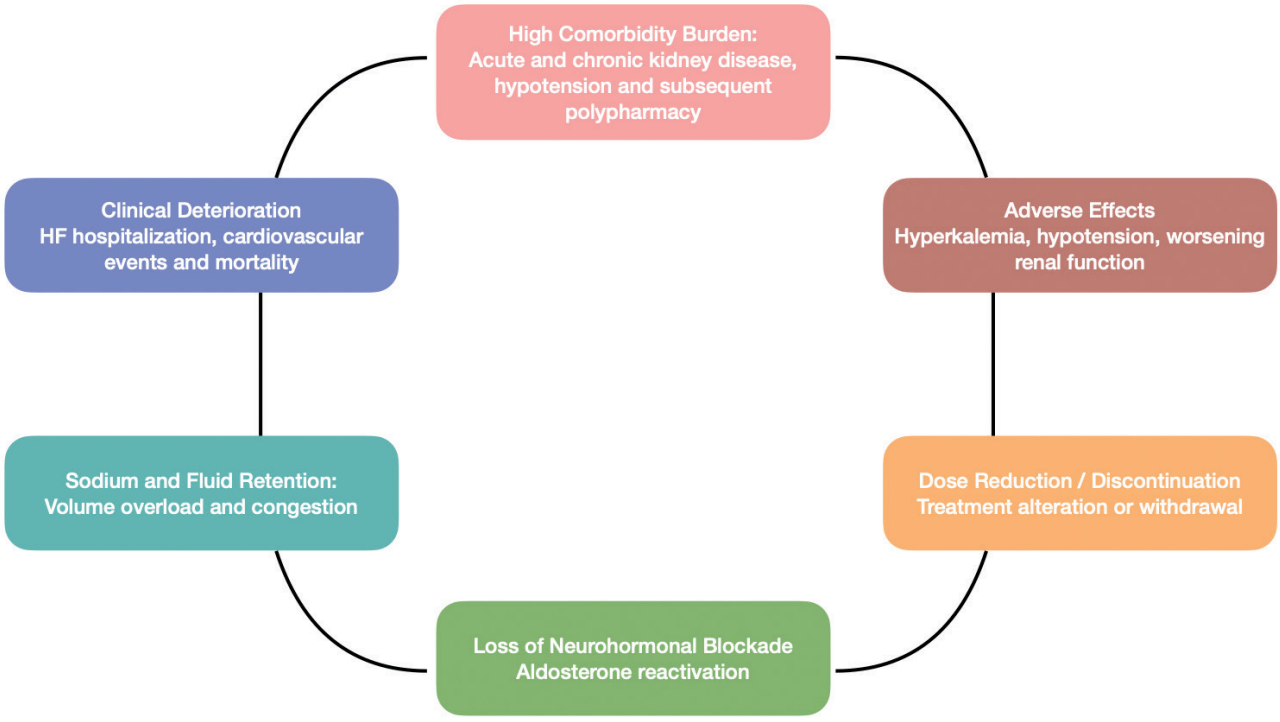

Figure 1. Cycle leading to loss of treatment durability in heart failure with preserved ejection fraction and heart failure with mildly reduced ejection fraction. High comorbidity burden predisposes to adverse effects, prompting dose reduction or discontinuation, leading to loss of neurohormonal blockade, fluid retention, and clinical deterioration, perpetuating a self-reinforcing cycle.

The notion that treatment continuity is integral to therapeutic benefit is not unique to steroidal MRAs. This problem was first investigated in the blinded withdrawal analyses of the EMPEROR studies evaluating empagliflozin across the whole spectrum of HF, in which discontinuation of therapy was clearly associated with early worsening of outcomes, underscoring the importance of sustained treatment exposure. Notably, however, for sodium-glucose cotransporter 2 inhibitors (SGLT2i), this represents less of a practical limitation,[21] as rates of treatment discontinuation are comparatively low in both clinical trials and real-world settings.[17,18] This concept is further reinforced by emerging evidence on the blinded withdrawal phase in recent trials of non-steroidal MRA therapy. In the FINEARTS-HF program, discontinuation of finerenone after long-term treatment was associated with a rapid attenuation of benefit and a marked increase in cardiovascular events, particularly HF related hospitalizations.[19,20] These findings suggest that sustained neurohormonal modulation is required to maintain clinical stability, and that withdrawal may lead to rebound pathophysiological activation, including heightened aldosterone activity and adverse hemodynamic shifts.[17-20]

Clinical practice

From a clinical perspective, these findings carry important implications for therapeutic decision-making. When initiating any kind of MRA therapy, clinicians must consider not only the well-recognized risk of adverse effects, such as hyperkalemia and hypotension,[22] but also the potential consequences of treatment discontinuation. In complex, multi-morbid patients, cessation of therapy is rarely benign and may reflect a state of clinical instability while simultaneously contributing to further deterioration through loss of neurohormonal modulation.[3,12] Accordingly, prescribing decisions should extend beyond the binary assessment of drug initiation and instead incorporate the likelihood of sustained treatment, the patient's capacity to tolerate therapy over time, and the risks associated with interruption. This nuanced approach is particularly relevant in HFpEF and HFmrEF populations, in whom vulnerability is high and therapeutic margins are narrow, underscoring that the clinical impact of a therapy may depend as much on its durability as on its efficacy (Figure 2).[3]

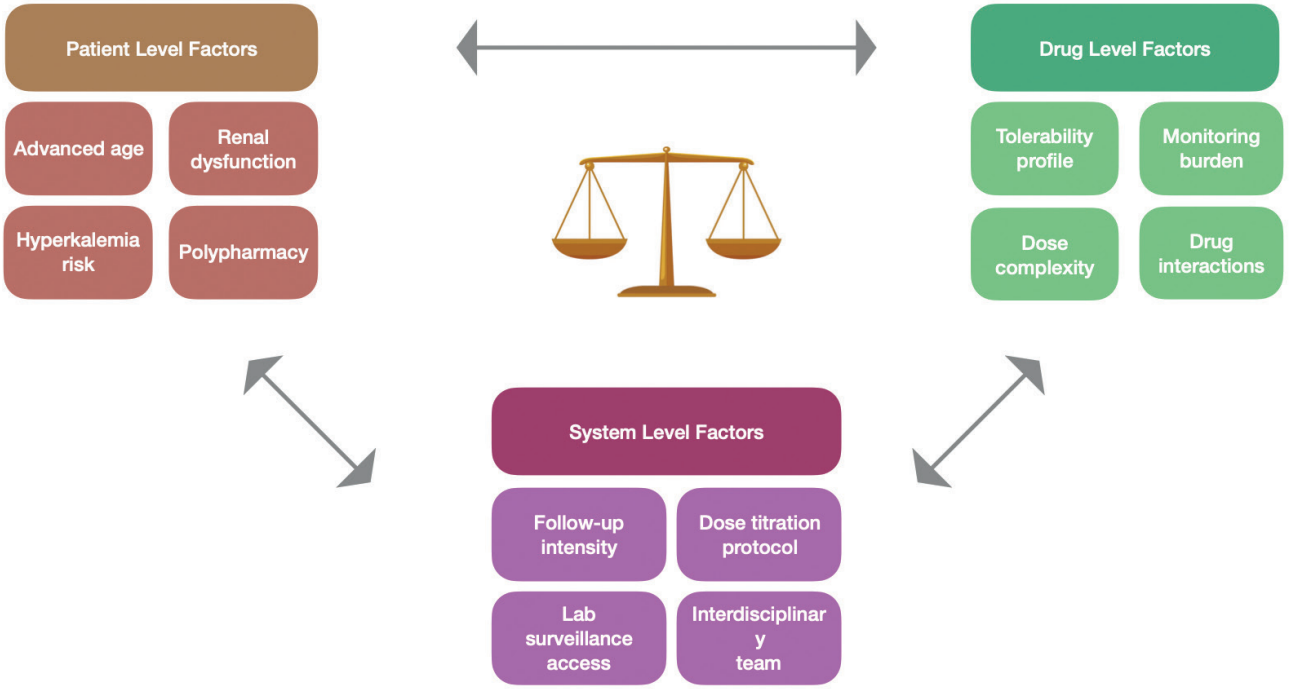

Figure 2. Multilevel determinants of treatment durability in heart failure with preserved ejection fraction and heart failure with mildly reduced ejection fraction. Treatment durability reflects the interplay of patient factors, drug characteristics, and system-level care processes, which together influence tolerability, adherence, and persistence of therapy.

Contributions

All the authors made a substantive intellectual contribution, read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest

The authors declare no potential conflict of interest.

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