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Perspectives

Increasing Evidence Supports the Benefits of Rapid Uptitration of the Neurohormonal Blockade in HFmrEF/HFpEF Patients With AHF

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Despite evidence that the neurohormonal and adrenergic systems are significantly activated in heart failure (HF) patients with mildly reduced (HFmrEF) or preserved (HFpEF) ejection fraction (EF), many studies examining the use of neurohormonal and adrenergic blockers in these populations failed to show substantial benefits.[1] This activation is likely to be even higher in acute HF (AHF) settings or the peridischarge phase of the disease than in a stable, chronic HF state. Thus, one may speculate that the potential benefits of the neurohormonal blockade might be higher in the peridischarge period.

No large prospective studies have evaluated the effects of either beta-blockers (BBs) or angiotensin-converting enzyme inhibitors in patients with an EF of >40%.[2] However, some data exist with respect to other guideline-directed medical therapy components (Table 1).

Angiotensin receptor blockers were found to have positive effects in CHARM-PRESERVED (Effects of Candesartan in Patients With Chronic Heart Failure and Preserved Left-ventricular Ejection Fraction), which recruited a chronic HFpEF population.[3] In the CHARM Program, even though candesartan's effect on the primary end point was not significant in HFpEF, the risk of recurrent HF hospitalization was significantly lower in the candesartan group, even in patients with preserved EF,[4] suggesting that, in those patients, candesartan had protective effect only after an AHF admission. I-PRESERVE (Irbesartan in Heart Failure with Preserved Ejection Fraction Study), which examined the other angiotensin receptor blocker irbesartan, did not show its clinical benefit in stable HFpEF patients.[5]

With regards to mineralocorticoid receptor antagonists (MRA), although TOPCAT (treatment of preserved cardiac function heart failure with an aldosterone antagonist) did not significantly reduce the incidence of the primary composite outcome in patients with an left ventricular EF of ≥45%,[6] it did have a small effect when inappropriately enrolled patients in Georgia and Russia were excluded.[7] In contrast, FINEARTS-HF (Finerenone in heart failure with mildly reduced or preserved ejection fraction) recently showed that finerenone reduced the primary composite end point of total worsening HF events or cardiovascular death compared to placebo in patients with an EF of ≥40%.[8] However, subsequent analysis has shown that the effects were entirely driven by treatment effects in patients close to an AHF admission, especially those within 7 days of such an admission, while the effects were very small to neutral in patients >3 months from an AHF admission.[9]

With respect to angiotensin-neprilysin inhibitors, PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction) failed to meet its primary end point,[10] total hospitalizations for HF and death from cardiovascular causes;

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Table 1 The Impact of Different HF Therapies on Outcomes in AHF vs. CHF in Patients With Mildly Reduced or Preserved EF

	AHF	CHF
Beta-blocker	No RCT data	No RCT data
Angiotensin enzyme-converting inhibitor	No RCT data	No RCT data
Angiotensin receptor blocker	CHARM-Program Among patients with previous HF hospitalization: The impact on the primary outcome (cardiovascular death or HF hospitalization) HRs: 0.48 in HFmrEF (95% CI 0.33−0.70, $P < .001$), 0.78 in HFpEF (95% CI 0.59−1.03, $P = .08$)	CHARM-PRESERVED No effect on the primary outcome (cardiovascular death or HF hospitalization) Lower risk of HF hospitalizations 0.84 (5% CI 0.70−1.00) $P < .05$, No Impact on CV death
Angiotensin-neprilysin inhibitors	PARAGON-HF Patients post HF episode (≤30 days) Absolute risk reduction 6.4%	PARAGON-HF No effect on the primary composite outcome Never hospitalized Absolute risk reduction −0.02%
MRA	FINEARTS-HF Finerenone lowered the risk of the primary composite outcome in those enrolled within 7 days of WHF (RR 0.74, 95% CI 0.57−0.95) or between 7 days and 3 months of WHF	TOPCAT No effect on the primary composite outcome HR: 1.78 (95% CI 1.48−2.13, $P < .001$) in the Americas cohort FINEARTS-HF No impact on the primary outcome among patients >3 months from WHF or without prior WHF (RR 0.99, 95% CI 0.81−1.21)
Comprehensive neurohormonal blockade (beta-blocker, RASi, MRA)	STRONG-HF The primary composite end point in patients with EF >40% The risk difference 12.5% (95% CI 3.7%−21.3%)	

AHF, acute heart failure; CHF, chronic heart failure; CI, confidence interval; CV, cardiovascular; EF, ejection fraction; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFmrEF, heart failure with midrange ejection fraction; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist; RASi, renin−angiotensin system inhibitor; RCT, randomized, controlled trial; RR, risk ratio; WHF, worsening heart failure.

however, most patients enrolled in PARAGON-HF were enrolled during the stable phase of chronic HF. However, a significant effect was observed in PARAGON-HF in patients enrolled closer to an AHF, although the *P* value for interaction was .15.[11] This finding was confirmed by a recent prespecified meta-analysis of the PARAGON-HF and PARAGLIDE-HF (Prospective comparison of ARNI with ARB Given following stabiLization In DEcompensated HFpEF) studies,[12] which showed significant effects in patients close to an AHF event.

Finally, a subanalysis of STRONG-HF (Safety, Tolerability, and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies) that examined the role of rapid uptitration of guideline-directed medical therapy, mostly inclusive of RASi, BB, and MRAs, has found large effects of this strategy in patients with AHF and an EF of >40%, with the effects numerically even surpassing those seen in patients with an EF of ≤40%.[13] The primary composite end point in STRONG-HF in patients with an EF of >40% (i.e., HFmrEF and HFpEF) occurred in 10.7% in the high-intensity care group and in 23.3% in the usual care group (risk difference 12.5%, 95% CI 3.7%−21.3%). Of note, in FINEARTS-HF, the incidences of first HF readmission or death in patients enrolled within 7 days of an AHF event (similar to the inclusion criteria in the STRONG-HF study) were 13.5 events/100 patient-years in the finerenone arm vs 16.3 events/100 patient-years in the control arm. Although cross-study comparisons are not possible, the patients enrolled in the STRONG-HF study were simultaneously up-titrated on three types of therapy (RASi, BBs, and MRAs), whereas in FINEARTS-HF they were only given MRA vs placebo; therefore, it is possible that the greater effect size observed in STRONG-HF may be due to the fact that 3 medications addressing neurohormonal and adrenergic activations were given simultaneously. Therefore, the results of FINEARTS-HF in patients close to an AHF episode are similar, although smaller in magnitude, to those observed in the STRONG-HF patients with HFmrEF and

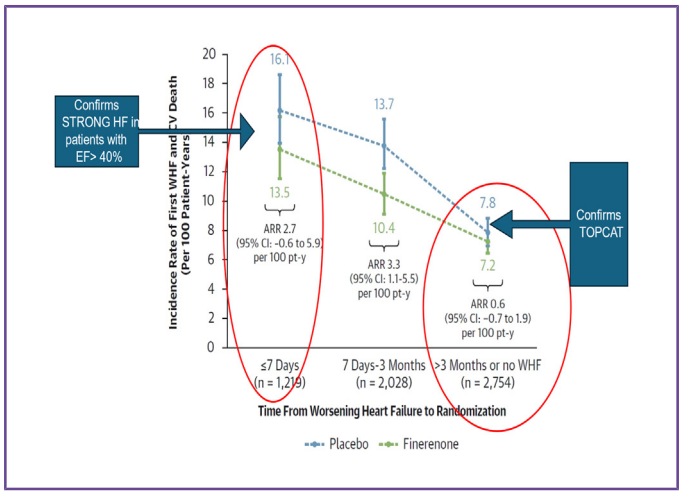

Fig. 1. Results of the FINEHEART-HF study by time from acute heart failure (AHF) event. ARR, adjusted risk ratio; CI, confidence interval; EF, ejection fraction; WHF, worsening heart failure.

HFpEF (Fig. 1), although the data on the effects of finerenone in FINERARTS-HF in patients who were enrolled >3 months from an AHF admission are very similar to those from TOPCAT.

Of note, retrospective data from observational studies in AHF showed a significant reduction in mortality in patients treated with RASI and BB. The results of the largest AHF meta-analysis, using data from the 285 studies and including >15 million AHF hospitalizations demonstrated the association between increased use of BB and RASIs at hospital admission for AHF with any EF and reduction in mortality.[14] The results were replicated in another study, where BBs and RASIs at discharge, alone or in combination, were associated with a consistent reduction in mortality in patients with recent AHF, regardless of left ventricular EF or the presence of comorbidities.[15]

One must contextualize the current results vis-à-vis the effects observed in stable, chronic HF with HFmrEF/HFpEF patients treated with sodium-glucose cotransporter (SGLT) inhibitors and, recently, glucagon-like peptide-1 receptor agonists, both of which have exerted highly beneficial effects in stable chronic HF patients with high EF.[16–20] SGLT inhibitors were also shown to be effective in AHF with HFmrEF and HFpEF patients,[21,22] with empagliflozin being shown in EMPULSE (Empagliflozin in Patients Hospitalized for Acute Heart Failure) to be effective across the full EF spectrum in patients with AHF.[23] Therefore, SGLT inhibitors and glucagon-like peptide-1 agonists are probably effective in HFmrEF and HFpEF in chronic HF patients. For SGLT inhibitors, evidence already exists that they are also effective in AHF patients and, therefore, should be started during or immediately after an AHF event.[21,22]

Taken together (Fig. 2), these results suggest that the effectiveness of treatment of patients with AHF and HFmrEF or HFpEF, both angiotensin-neprilysin inhibitors and MRA/finerenone may be through targeting neurohormonal activation, which is particularly activated in AHF. A combination of angiotensin-neprilysin inhibitors/MRA-finerenone/SGLT2i as a potentially optimal approach to be started as early possible after stabilization across the whole spectrum of left ventricular EF. The results of STRONG-HF suggest that combining those drugs may further add to the benefit of each of these therapies, especially when uptitrated rapidly. The same conclusion is not well-supported by available data in patients with HFmrEF and HFpEF who are in the chronic HF phase (>3 months from an AHF event), where neurohormonal activation is expected to be smaller, with both the results of PARAGON-HF and FINEARTS-HF suggesting smaller effect sizes, also supported by the smaller effect sizes observed in CHARM-PRESERVED, I-PRESERVE, and TOPCAT in chronic HF patients. In those patients, treatment with SGLT inhibitors and glucagon-like peptide-1 receptor agonists may be of higher value. How long neurohormonal blockers will be effective in patients with HFmrEF and HFEPF is not clear. In STRONG-HF, the patients were followed for 180 days, and the effects seemed to continue and diverge over time; the same can be said about FINEARTS-HF, where visual examination of the Kaplan–Meier curves suggests that the curves continue to diverge over the first year, at least. Therefore, it seems that neurohormonal blockade should be given to patients with HFmrEF and HFEPF for ≥1 year after an AHF admission and beyond.

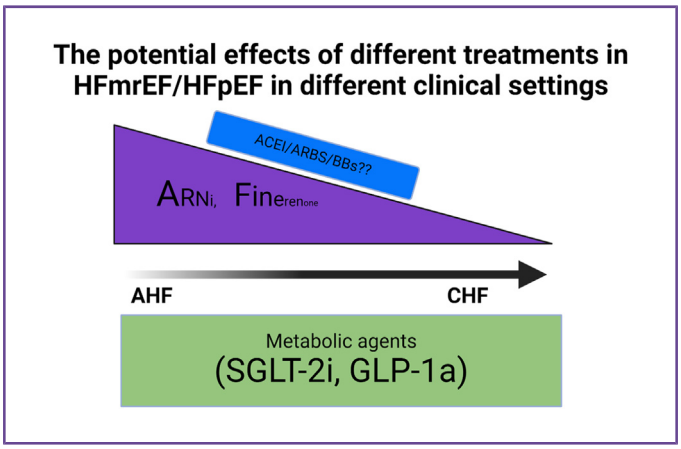

Fig. 2. Effects of medications on outcomes in acute heart failure (AHF) and chronic heart failure (CHF) owing to HF with midrange ejection fraction and HF with preserved ejection fraction. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin-neprilysin inhibitor; BB, beta-blocker; GLP-1a, glucagon-like peptide 1a; SGLT-2i, sodium-glucose cotransporter 2 inhibitor.

Those contrasting results highlight the differences between AHF and chronic HF patients, especially those with HFmrEF/HFpEF. In the acute state, where neurohormonal–adrenergic activation is more pronounced, rapid uptitration of quadruple guideline-directed medical therapy is now well-supported by evidence from prospective clinical trials and should be adopted by guidelines and implemented.

Disclosures

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CRediT authorship contribution statement

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