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All-Cause Mortality as an End Point for Heart Failure With Preserved Ejection Fraction: Underperformance or Overambitious?

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EMPEROR-PRESERVED, which examined sodium-glucose co-transporter 2 inhibitor empagliflozin, is the first study among patients with heart failure with preserved ejection fraction (HFpEF) to meet its primary end point.[1] This is a major development for patients with HFpEF and the broader scientific community; all previous studies in HFpEF have failed to meet their primary end point. This includes the phase III clinical trials of sacubitril-valsartan and spironolactone, which served as the foundations for endorsement as treatment for HFpEF by the US Food and Drug Administration, despite failing to meet their prespecified primary end points. Given this historical context, it is likely that empagliflozin will also receive US Food and Drug Administration endorsement. However, based on early chatter on media outlets including Twitter, this endorsement will not occur without debate and controversy.

One of the early critiques of the EMPEROR-PRESERVED results was that empagliflozin did not decrease all-cause mortality. Naturally, many compare this study with other studies in HF that have met their primary end point. However, such prior studies enrolled patients with HF with reduced ejection fraction (HFrEF) and included a younger cohort than that studied in EMPEROR-PRESERVED. These distinctions are important and raise concern about the appropriateness of comparing EMPEROR-PRESERVED to these prior studies.

Whereas the pathophysiology of HFrEF is primarily driven by neurohormonal activation even across different etiologies, the pathophysiology of HFpEF is highly heterogeneous with varied mechanisms that span numerous cardiovascular domains and multiple organ systems.[2] Accordingly, single agents (including empagliflozin, which has multiple targets relevant to HFpEF), may have modest effects when compared with agents targeting neurohormonal pathways in HFrEF.

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The mean age of landmark pharmacologic studies in HFrEF have been in the low to mid 60s, whereas the mean age of EMPEROR-PRESERVED was approximately 72 years (Table 1). This difference reflects contemporary intentionality to include older adults in clinical trials, and also reflects the fact that most patients with HFpEF are older adults with multiple comorbid conditions, along with notable geriatric conditions like polypharmacy, cognitive impairment, and frailty.[3] This point is especially relevant when considering clinical trial end points like all-cause mortality. Indeed, multimorbidity and concurrent geriatric conditions contribute to the risk of competing causes of death. In other words, patients with serious medical conditions other than HFpEF can die as a consequence of these other conditions, unrelated to the disease of HFpEF and unrelated to the therapy under investigation. Since treating HFpEF will not directly address these other causes, it is intrinsically more challenging for any HFpEF drug to decrease all-cause mortality.

The presence of a complex pathophysiology and competing causes of death does not mean that we should abandon all-cause mortality as an end point for HFpEF studies. Studies like the recently completed Dapagliflozin Evaluation to Improve Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) will provide additional insight on the impact of sodium-glucose co-transporter 2 inhibitor on all-cause mortality. However, regardless of those results, these inherent challenges of improving all-cause mortality are important to consider when interpreting clinical trials in HFpEF. In our opinion, the absence of mortality reduction on a population-level should not undermine the potential impact of a therapy for HFpEF, particularly when fully considering end points that may be important to patients suffering from this condition. For example, hospitalization for HF may be a particularly relevant end point, given the harm associated with such an event. Indeed, overall survival decreases with each subsequent hospitalization for HF.[4] With hospitalization, there is also an increased risk for being discharged to a nursing home and losing independence—an event that many older adults fear more than death itself.[5] Although hospitalization is certainly a marker of illness severity, the hospitalization itself may contribute to observed decreases in survival, independence, and quality of life. Posthospitalization syndrome has been defined as a state of vulnerability in the period immediately after hospital discharge when there is a heightened risk of disability, morbidity, mortality, and rehospitalization and may have a disproportionate impact in older adults who already contend with deficits in cognition and function (i.e., patients with HFpEF). Taken together, medications that can decrease HF hospitalizations (even in the absence of decreasing other causes of hospitalizations) provide significant value to patients with HFpEF.

HFpEF has been a challenging condition to understand and ultimately treat. In the context of multiple clinical trials that have failed to meet their primary end points, HFpEF is understood to be a complex heterogeneous condition that requires a phenotype-matching approach to treatment.[2] However, there is another lesson to be learned here, which has emerged from the early discussions about the EMPEROR-PRESERVED study—all-cause mortality may be an overambitious clinical end point in HFpEF. Patient-reported outcomes like quality of life and functional capacity have considerable value to patients, especially older adults who may prioritize these outcomes over longevity.[6] We thus advocate for patient-centered outcomes such as these, as well as emerging concepts like days at home, or home time, as reasonable clinical end points for future trials. We hope that ongoing

discussions about the EMPEROR-PRESERVED study will re-emphasize the importance of patient-centered end points beyond all-cause mortality, and subsequently guide future clinical trial design for HFpEF.

Disclosures

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Table 1.

HFpEFmortality

Drug	Study	Mean Age	Primary End Point Met?	Reduction in Mortality?	Endorsed by FDA?
Heart failure with reduced ejection fraction					
Beta-blocker	MERIT-HF	64 years	✓	✓	✓
	COPERNICUS	63 years	✓	✓	✓
ACEI	SOLVD	61 years	✓	✓	✓
ARNI	PARADIGM-HF	64 years	✓	✓	✓
MRA	RALES	65 years	✓	✓	✓
H-ISDN	A-HEFT	57 years	✓	✓	✓
Heart failure with preserved ejection fraction					
ARB	CHARM-PRESERVED	67 years	×	×	×
MRA	TOPCAT	69 years	×	×	✓
ARNI	PARAGON-HF	73 years	×	×	✓
SGLT-2i	EMPEROR-PRESERVED	72 years	✓	×	?

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; FDA, Food and Drug Administration; H-ISDN, hydralazine-isosorbide dinitrate; MRA, mineralocorticoid receptor antagonist; SGLT-2i, sodium-glucose cotransporter-2 inhibitor.