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EDITORIAL

The Emperor-Preserved trial: what will change for patients with heart failure with preserved ejection fraction?

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With the presentation of the Emperor-Preserved trial at the 2021 European Society of Cardiology (ESC) Congress and its subsequent publication,[1] the cardiology world breathed a sigh of relief that—at last—a drug had been shown to improve outcomes in patients with heart failure with preserved ejection fraction (HFpEF). The primary composite endpoint of cardiovascular death and HF hospitalization was reduced in patients on empagliflozin compared to placebo [hazard ratio (HR) 0.79, 95% confidence interval (CI) 0.69–0.90; $P < 0.001$], driven by a significant decrease in HF hospitalization (HR 0.71, 95% CI 0.60–0.83; $P < 0.001$). Cardiovascular death was not significantly different between groups. The result was irrespective of diabetes status. All-cause mortality was identical for the empagliflozin and placebo groups: 14.1% and 14.3%, respectively, and all-cause hospitalization was not reduced by empagliflozin. Two-thirds of the sample met the ESC criterion for ejection fraction (EF) ≥50% as one of the criteria for HFpEF, while 33% had an EF in the mildly reduced range (40–49%). Subgroup analyses by EF showed a diminution of effect as EF increased, so that above 60% the HR was not significant (0.87, 95% CI 0.69–1.10).[1]

Other drugs have come close, both spironolactone and sacubitril–valsartan reported modest non-significant effects on outcomes in patients with HFpEF, but indications for use of these drugs has relied on findings from subgroup analyses.[2,3] A *post hoc* subgroup analysis of the 1767 participants from the Americas in the TOPCAT trial showed a significant reduction in the primary composite outcome of cardiovascular mortality and HF hospitalization for those on spironolactone (HR 0.82, 95% CI 0.69–0.98; $P = 0.026$).[2] The PARAGON trial randomized 4822 patients with HFpEF to sacubitril–valsartan or valsartan. The primary composite outcome (cardiovascular death + HF hospitalization) missed significance (HR 0.87, 95% CI 0.75–1.01; $P = 0.06$) despite a 15% reduction in HF hospitalization.[3] However, a pre-specified subgroup analysis of patients with an EF less than the median of 57% found 22% reduction in the primary endpoint compared to those with an EF above the median.

Will the evidence for effective drug therapy in HFpEF prompt greater interest and expertise in diagnosing and managing patients with HFpEF? There are many challenges to overcome if it does. First, HFpEF remains under-recognized and challenging to diagnose, especially in primary care where patients often first present with symptoms and signs of HF.[4,5] Limited knowledge and lack of specific pharmacotherapy has led to inertia in identifying and managing patients with HFpEF among some healthcare practitioners.[5] Patients with HFpEF may have limited access to specialist support, including heart failure specialist nurses (HFSN), which may be due to policy but frequently due to a lack of capacity to see more patients. This dearth of awareness, difficulty in diagnosis, heterogeneity in patients, lack of specific treatment, and limited access to specialist services have all combined to make HFpEF a 'stealth syndrome', in other words often hidden from view and consideration.[6] A quick search of papers in EJCN 2019–21 found few specifically focusing on HFpEF,[7,8] although many others included both patients with HFpEF and HF with reduced ejection fraction (HFrEF).

Another essential issue to address in managing patients with HFpEF is that of multimorbidity. Although there is heterogeneity among patients with HFpEF, the prevailing phenotype is an older and multimorbid patient, with poor functional status and high prevalence of geriatric syndromes such as frailty.[4,7,9] Heart failure with preserved EF is thought to be driven by proinflammatory conditions such as obesity, hypertension, and diabetes, leading to systemic microvascular endothelial inflammation and dysfunction, fibrosis, remodelling of the left ventricle and impaired oxygen uptake in skeletal muscle.[4] Management of comorbidities remains a key component to treating patients with HFpEF. Comorbid conditions are a frequent cause of hospitalization and mortality among patients with HFpEF and contribute more to morbidity and mortality in HFpEF than in HFrEF.[10]

The challenge of HFpEF then is two-fold. Related to heart failure, we need greater awareness of HFpEF, understanding how it differs from HFrEF and what treatments are effective, and organizing

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systems of care to support diagnosis and management of these patients despite resource constraints. Specific, clear and easily accessed information about HFpEF as a distinct entity is needed for patients and providers. With appropriate systems of care identifying patients with HFpEF, newer drugs and other therapies can be delivered to patients. Second, but just as important, we need to consider the holistic management of patients with HFpEF who have multimorbidity, geriatric syndromes, and frequently poor physical function.

What is the role of the HFSN in managing patients with HFpEF? Should they simply be added to HFSN caseloads and if so, what education and advice is needed? If HFSN are to assume more responsibility for patients with HFpEF who have limited pharmacological and device HF treatment options, then more skill may be required in assessing and managing geriatric syndromes and comorbidities and liaising with other specialties and primary care to provide a collaborative holistic plan of care. These skills are part of the HFSN repertoire, but more emphasis may be needed in HFpEF. The increasing prevalence of HFpEF could also lead to greater responsibility for nurses in primary care and other community settings with the HFSN providing education and specialist support.

Inevitably, increased interest in HFpEF will follow in the wake of Emperor-Preserved demonstrating the effectiveness of empagliflozin in patients with HFpEF. But for patients to benefit from new drugs, and indeed from self-management support and rehabilitation, we need systems of care that provide needed information, support diagnostic procedures, and provide appropriate management and clinical services. HFpEF is increasing in prevalence relative to HFrEF[4] and has long been an under-recognized and often poorly managed condition. Now that the spotlight from Emperor-Preserved is shining on HFpEF, we need to ensure that we can deliver optimal care to this vulnerable group. Heart failure specialist nurses and other nurses and allied health professionals can and should have a major role to play in both practice and research.

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