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SGLT2 inhibitors - the first successful treatment for HFpEF?

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There is anticipation and expectation, rather than hope, that 2021 will see the first positive trials in heart failure with preserved ejection fraction (HFpEF). EMPEROR-Preserved and DELIVER (with the sodium-glucose co-transporter 2 (SGLT2) inhibitors empagliflozin and dapagliflozin, respectively) will shortly reach their conclusions. Cardiologists are confident that HFpEF will be added to the lengthening list of conditions where SGLT2 inhibitors have major benefits.

In this issue of the European Journal of Heart Failure, Anker and colleagues unveil the baseline characteristics of the EMPEROR-Preserved trial. In EMPEROR-Reduced, the sister trial in patients with HF and reduced ejection fraction (HFrEF), empagliflozin reduced the primary end point of heart failure (HF) hospitalisation and cardiovascular death.¹ If EMPEROR-Preserved is positive, there will be, for the first time, evidence that a drug improves outcomes across the full range of ejection fraction in patients with HFrEF and HFpEF.

What is the reason that clinicians and trialists are so confident that EMPEROR-Preserved will be positive? Speculating that a HFpEF trial will be positive sounds overly optimistic or even foolish. The last 25 years have seen a regular stream of neutral HFpEF trials. Many potential therapies, with theoretically attractive mechanisms of action, have failed. In the absence of positive trials, regulators are currently considering licensing drugs (sacubitril/valsartan and spironolactone) that have, albeit narrowly, missed their primary end points.^{2,3} The main reason why there is confidence is that SGLT2 inhibitors have proven to be successful in a host of clinical trials in disease areas which are closely related to HFpEF.

SGLT2 inhibitors have proven to reduce clinical events in patients with diabetes at high risk of or with established cardiovascular disease,⁴ HFrEF,^{1,5} chronic kidney disease (CKD),^{6,7} and hospitalised HF.⁸ Diabetes and CKD were both very common in the EMPEROR-Preserved population: 49% had diabetes and 50% had an eGFR of <60 ml/min/1.73m² (24% an eGFR <45 ml/min/1.73m²). The salutary effects of SGLT2 inhibitors in populations with diabetes and CKD suggest that a reduction in clinical events is likely in HFpEF. The benefit of SGLT2 inhibitors in HFrEF trials was seen regardless of baseline left ventricular ejection fraction (LVEF).⁹ It seems likely that this benefit will not halt abruptly at an LVEF of 40%, but extend above this. EMPEROR-Preserved included patients with an LVEF of $>40\%$. This is in contrast to recent HFpEF trials which enrolled patients with higher LVEFs (e.g. PARAGON-HF $\geq 45\%$).² The inclusion of LVEFs 40-45% increases the likelihood of a positive trial. This difference is reflected in the mean LVEF in EMPEROR-Preserved (54%) which is lower than recent HFpEF trials. Moreover, in trials of patients with diabetes, in the subgroup of patients with HF in whom there was information relating to LVEF or HF phenotype, the benefits of SGLT2 inhibitors were consistent across the HF spectrum.^{10,11}

The most encouraging data with respect to SGLT inhibitors in HFpEF came from the first trial in patients with hospitalised HF: the SOLOIST-WHF trial with the combined SGLT1 and 2 inhibitor sotagliflozin.⁸ This trial reported a reduction in the primary endpoint of total HF hospitalisations and cardiovascular deaths in 1222 hospitalised HF patients with diabetes. In the small subgroup of patients with HFpEF (n=256), a reduction in the primary endpoint was

seen (HR 0.48 (95% CI 0.27-0.86). SOLOIST-WHF gave us a strong hint that EMPEROR-Preserved and DELIVER (NCT03619213) will be the first positive trials in HFpEF.

If EMPEROR-Preserved is a positive trial, can we postulate what the results will be? In trials of diabetes, CKD and HFrEF, SGLT2 inhibitors have consistently reduced HF hospitalisations and improved renal outcomes.^{1,4-7} Most would be surprised if both HF and renal outcomes were not improved in HFpEF. Patients and clinicians are excited that quality of life might be improved in HFpEF as it is in HFrEF.^{1,12} Whether or not mortality will be reduced by SGLT2 inhibitors in HFpEF is unclear. Different effects on mortality have been reported throughout large randomised controlled trials in different populations over the last 6 years. We can remain hopeful that this large trial (n=5988) might report a reduction in cardiovascular (if not all-cause) mortality, however the competing risk of non-cardiovascular mortality in an elderly and co-morbid population makes this a high hurdle to clear.

HFpEF is known to be a broad church comprised of heterogeneous conditions. Some patients have atrial fibrillation (AF) driving their condition (52% in EMPEROR-Preserved had a history of AF or atrial flutter), others hypertensive heart disease (90% had hypertension), others obesity (45% had a body mass index >30 kg/m²) and others will have been post-aortic valve replacement patients with hypertrophy and fibrosis. Many other subgroups exist, and many patients have multiple concomitant drivers of HFpEF. For EMPEROR-Preserved to be positive, SGLT2 inhibitors need to be effective against a wide variety of pathologies. While we are confident that patients with HFpEF and diabetes and CKD will benefit, what will be the effect of empagliflozin on HFpEF driven by AF, hypertension, obesity or other causes of HFpEF? Once the trial is published, we eagerly await secondary analyses investigating the effects of SGLT2 inhibitors in these sub-populations. One of the remarkable observations of recent years is that defining HFpEF is a challenge, and that different methods of classifying patients result in very different numbers of people receiving a label of HFpEF. When patients were assigned a diagnosis of HFpEF based on 2 different scoring systems (H₂FPEF or HFA-PEFF scores), very different numbers of patients were given a HFpEF diagnosis.¹³ Will SGLT2 inhibitors be equally efficacious across all definitions, categories and subgroups of patients with HFpEF?

Although mechanistic trials of SGLT2 inhibitors in HFpEF are scarce,¹⁴ there is some evidence that this class of drug has several properties that may prove effective in HFpEF. Blood pressure-lowering, weight loss and anti-inflammatory properties may improve the HFpEF syndrome.¹⁵ Although previous SGLT2 inhibitors trials have shown that the reduction in clinical outcomes across populations is independent of glucose lowering,¹⁶ it is conceivable that patients with HFpEF and diabetes have even more to gain from SGLT2 inhibitors than patients with HFpEF without diabetes. Some patients enrolled in EMPEROR-Preserved might have what has been termed “diabetic cardiomyopathy” although the meaning of this term is still debated, confused and unclear.¹⁷ A reduction in glycaemia-related, deleterious cardiovascular mechanisms might improve cardiac function and outcomes.

Why do we have separate trials of patients with HFrEF and HFpEF? Most cardiologists are increasingly frustrated by the role that LVEF has in governing who does and does not receive HF therapies. The pivotal role which LVEF has assumed reflects the design of clinical trials

which have created the dichotomy of HF with reduced and preserved EF. Several aspects of the reign of LVEF frustrate clinicians and triallists. The measurement error of between 5-10% makes a mockery of the use of LVEF to categorise individual HF patients. The same patient might be assigned an LVEF of 39%, 42% or 46% on the same day if assessed by different imagers or different imaging modalities. The concept of HF with mid-range EF is even more difficult to comprehend. Given the limitations of its measurement, how can such a narrow range of LVEF identify a clinically meaningful population? Trials in HFpEF have chosen different lower boundaries of LVEF as inclusion criteria (e.g. >40%, >45% or >50%). Dissection of clinical trials of various agents in HF have recently uncovered beneficial effects of most HF therapies up to an of LVEF 55-60%.^{18,19} In retrospect, if patients with HF had been included in trials regardless of LVEF (or up to 55-60%), patients would be benefitting from many therapies that “failed” in populations described as HFpEF. It is conceivable that angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, sacubitril/valsartan, beta-blockers and mineralocorticoid receptor antagonists (MRAs) will all be recommended for patients with LVEFs up to 55-60% (or in other words, for all those who have left ventricular systolic dysfunction of any severity). It is fair to say that HFpEF trials have been hampered by the inclusion of some patients who probably do not have HF. These imposters usually have high LVEFs with some condition other than HF driving their clinical syndrome.

What criticisms could be aimed at EMPEROR-Preserved? Only 67% were taking a loop diuretic at baseline. It is common for a proportion of patients in HF trials not to be taking loop diuretics, but this number seems high. Some may expect the first step in the management of HF to be the prescription of a loop diuretic. On the other hand, 86% were taking a diuretic of any type. Secondary analyses of those on and off loop diuretics will be eagerly anticipated. 37% were taking an MRA at baseline (but this is more than other recent HFpEF trials e.g. PARAGON-HF 24%).² There is, as yet, no guideline-recommended (or evidence-based) reason why patients should be on MRAs, but MRAs may receive regulatory recommendation as a HFpEF therapy. Secondary analyses of the efficacy of empagliflozin in the presence and absence of MRAs will also be welcome.

The European Society of Cardiology guideline definition of HFpEF requires patients to have elevated natriuretic peptide levels along with evidence of structural heart disease (left ventricular hypertrophy (LVH) and/or left atrial (LA) enlargement) and/or diastolic dysfunction (e.g. elevated E/E').²⁰ The median baseline NT-proBNP level in EMPEROR-Preserved (974pg/ml) was slightly higher than that in both PARAGON-HF (885pg/ml) and TOPCAT (950pg/ml), perhaps reflecting the higher incidence of AF at screening and greater degree of renal dysfunction. In EMPEROR-Preserved, by echocardiography, 41% of patients had an LA width of <4 cm, 79% an LA length of <5cm, 20% an LA volume index of $\geq 34\text{ml/m}^2$ and 13% an E/E' of ≥ 13 . By means of comparison, in PARAGON-HF 59% of patients with available measurements had a LA volume index $>34\text{ml/m}^2$ and 37% a lateral E/e' of >13 .²¹ LVH by echocardiography was not recorded but by electrocardiographic analysis LVH was seen in only 10%, a lower prevalence than in all previous HFpEF trials. It is possible that patients in EMPEROR-Preserved did not have the major cardiac abnormalities that are commonly seen in HFpEF in clinical practice.

Only 23% of patients in EMPEROR-Preserved had a HF hospitalisation within 12 months. This is lower than other contemporary trials (e.g. PARAGON-HF 48%).² Will there be uncertainty as to the benefits of SGLT2 inhibitors in those who are hospitalised or recently hospitalised? As already discussed, SOLOIST-WHF included a small number of patients with hospitalised HFpEF. Some ongoing trials of hospitalised HF are excluding (DAPA ACT HF-TIMI 68 (NCT04363697)) or including (EMPULSE (NCT04157751)) HFpEF. Another criticism might be the exclusion of patients with “recovered” LVEF. This is a common clinical scenario with little evidence to guide management.

In conclusion, what HFpEF needs is a positive clinical trial and we are expectant that EMPEROR-Preserved, the largest clinical trial to date, will deliver it. A positive clinical trial will result in a major reason for clinicians to identify HFpEF and elevate its status. Fortunately, DELIVER (with dapagliflozin in HFpEF) will follow quickly; if these 2 trials are positive, the next decade will be celebratory times for patients with HFpEF.

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