Title: **Re-emergence of heart failure with a normal ejection fraction?**

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The two most novel aspects of the new ESC guidelines on heart failure were the strong recommendation given to sodium-glucose cotransporter 2 (SGLT2) inhibitors as a treatment for heart failure with reduced ejection fraction (HFrEF, LVEF ≤40%) and the first-ever recommendation of any therapy for the renamed heart failure and mildly reduced ejection fraction (HFmrEF, LVEF >40% to <50%).[1] Use of all the major neurohumoral modulating therapies was proposed in the latter patients, although the recommendation was much weaker than for patients with HFrEF because it was based on retrospective analyses of trials which suggested benefit of these treatments in certain patients with a LVEF >40% i.e., likely those with some degree of left ventricular systolic dysfunction.[2] The precise upper LVEF threshold above which there is no benefit is uncertain and the source of debate. However, it is still the case that no treatment other than diuretics is recommended in the ESC guidelines for patients with heart failure and a LVEF ≥50%.[1]

At the time of writing of the guidelines, the place of SGLT2 inhibitors in the treatment of patients with a LVEF >40% was uncertain. Recently, the Empagliflozin Outcomes Trial in Heart Failure and a Preserved Ejection Fraction trial (EMPEROR-Preserved) has provided the first robust evidence that SGLT2 inhibitors are valuable in the treatment of patients with a LVEF >40%, demonstrating a striking relative risk reduction of the primary composite outcome of cardiovascular death or heart failure hospitalization of 21 (95% CI 10-31)%, p<0.001.[3] This added to evidence from the corresponding trial with empagliflozin in patients with HFrEF (EMPEROR-Reduced) in which the same outcome was reduced by 25 (14-35)% in patients with a LVEF ≤40%, p<0.001.[4] With the completion of their second landmark trial, the EMPEROR investigators were perfectly placed to explore the effects of empagliflozin across the spectrum of LVEF, as had been done for neurohumoral modulating therapies.[2,5]

Despite the demonstration, overall, of the benefit of empagliflozin in a large cohort of patients with a LVEF >40% in EMPEROR-Preserved, Butler and colleagues question whether there is an upper LVEF threshold beyond which efficacy is lost.[6] The authors' key finding was that the effect of empagliflozin appeared to be attenuated in patients with a LVEF of >65% (**Figure 1**); the effect in the LVEF

categoreies examined post hoc was HR 0.73 (95%CI 0.55, 0.96), 0.63 (0.50, 0.78), 0.72 (0.52, 0.98), 0.66 (0.50, 0.86), 0.70 (0.53, 0.92) and 1.05 (0.70, 1.58) in those with a LVEF <25% (n=999), 25-34% (n=2230), 35-44% (n=1272), 45-54% (n=2260), 55-64% (n=2092), and >65% (n=865), respectively.

The first question to ask is whether these findings are true? Subgroup analysis is notoriously treacherous and post hoc subgroups are more so. LVEF is highly variable and is often measured imprecisely, with a strong digit preference frequently observed for multiples of 5. So already we are on thin ice! Although the authors had a huge dataset of 9718 patients, only 865 had a LVEF >65%. Among the 437 assigned to placebo, only 45 had a first hospitalization for heart failure (the focus of the authors' analysis). This is not a large enough number of events to give a robust estimate of the effect of treatment in this subgroup and the 95% confidence interval ranged from a potential 30% reduction to a 58% increase in risk. Importantly, the authors did not find a significant interaction between LVEF and the effect of empagliflozin (**Figure 1**). It is also hard to square these findings with the results of the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA-REG) OUTCOME trial in which empagliflozin treatment led to large reductions in both heart failure hospitalization and cardiovascular death in people with type 2 diabetes who presumably, in the main, had a normal LVEF (and half of the patients in EMPEROR-Preserved had type 2 diabetes).[7] We think all of this leaves uncertainty about whether there really is a loss of benefit in patients with a LVEF >65% (in addition to all the caveats about subgroups and measurement of LVEF). While the findings with neurohumoral modulating therapies make it tempting to surmise that the benefit of empagliflozin also diminishes as LVEF increases, we should wait on additional data before reaching this conclusion. Those data will soon be forthcoming from another large trial with an SGLT2 inhibitor in patients with a LVEF >40% i.e., the Dapagliflozin Evaluation to Improve the LIVEs of Patients with PReserved Ejection Fraction Heart Failure trial (DELIVER).[8] It might be a terrible error to prematurely and mistakenly conclude that SGLT2 inhibitors are not beneficial in patients with a normal LVEF, especially, as discussed below, other therapies may not help these patients.

But for the moment, let us assume we accept the authors' conclusion that the benefit of treatment does vary by LVEF. Here the authors raise the even more vexed question of whether this pattern of effect according to LVEF is different than seen with neurohumoral modulating therapies? With this, we are on even thinner ice, not only looking at post hoc subgroups but comparing them across trials! Such an assessment must be qualitative at best. Inspection of **Figure 2** suggests to us a broadly similar pattern of response.

If these analyses with both neurohumoral modulating therapies and empagliflozin, as well as digoxin are correct, they raise a much more important question than whether one treatment has a larger benefit than another[9], or whether the benefit of one treatment extends to a LVEF of 65% rather than 60%. The bigger question raised by these data is why HFmrEF continues to be defined as a LVEF of >40% to <50%? We know of no biological basis for this narrow range. Just as the "phenotype" HFrEF was defined by a series of trials identifying the patients who benefit from a variety of therapies, the same should apply to patients who appear to benefit in these recent analyses. If the data summarized in **Figures 1 and 2** really do reflect a true interaction between the effect of treatment and LVEF, then they indicate that the upper LVEF boundary for HFmrEF should be 55% (or maybe 60% in women, to reflect the apparent benefit to a higher LVEF in women[2]) i.e., around the lower limit of normal. If this interpretation is correct, persisting with the outdated description of heart failure with preserved ejection fraction (HFpEF) no longer makes sense – the word "preserved" was originally used to encompass all patients with a LVEF >40% ie., from a LVEF that was below normal, but not in the clearly reduced range, to a completely normal LVEF.[9] If HFmrEF is redefined as a LVEF of >40% to 55% or 60%, the only logical description for the syndrome affecting the remaining patients is "heart failure with a normal ejection fraction".[10,11] What the pathophysiological problem is in those patients and what treatments might help are key questions for future research in heart failure.

Figure legends

Figure 1: Influence of ejection fraction on the effect of empagliflozin on time to cardiovascular death or hospitalization for heart failure. Ejection fraction is analyzed as a continuous variable, based on the assumption that the relationship is linear (From Butler et al[6]). The key to the figure is as described in the legend to Figure 2.

Figure 2: Interaction between the effect of: A. the angiotensin receptor blocker (ARB) candesartan; B. the angiotensin receptor-neprilysin inhibitor (ARNI) sacubitril valsartan; C the mineralocorticoid receptor antagonists (MRA) spironolactone and eplerenone; and D. the digitalis glycoside digoxin according to baseline LVEF in the trials reported by Dewan et al[2] and the Digitalis Investigation Group.[12] The analysis was similar to that described in Figure 1. The X-axis shows LVEF and the Y-axis the hazard ratio (HR) for the effect of the experimental treatment compared with control therapy on the time-to-first occurrence of cardiovascular (CV) death or heart failure (HR) hospitalization. A HR below 1 indicates benefit. A HR of 1 is indicated by the horizontal solid line. The other solid line shows a continuous HR and the interrupted lines on either side of this the 95% confidence interval (in Figure 1 the 95%CI is indicated by the grey shaded area).

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