

EMPEROR Preserve and what it means

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Heart failure? What heart failure?

What William Harvey, in 1785, called dropsy [1] turned out to be heart failure with reduced ejection fraction (HFrEF), water retention and severe oedema of the lungs and peripheries [2]. He did not know what heart failure is, nor what the underlying cause of dropsy was. However, William Withering, for the first time, provided a drug – or rather herbs containing a drug – that induced diuresis and helped his patients substantially. For more than a century not much happened until diuretics appeared that allowed for even better control of oedema, but neither drugs have ever been shown to actually improve more than symptoms [3].

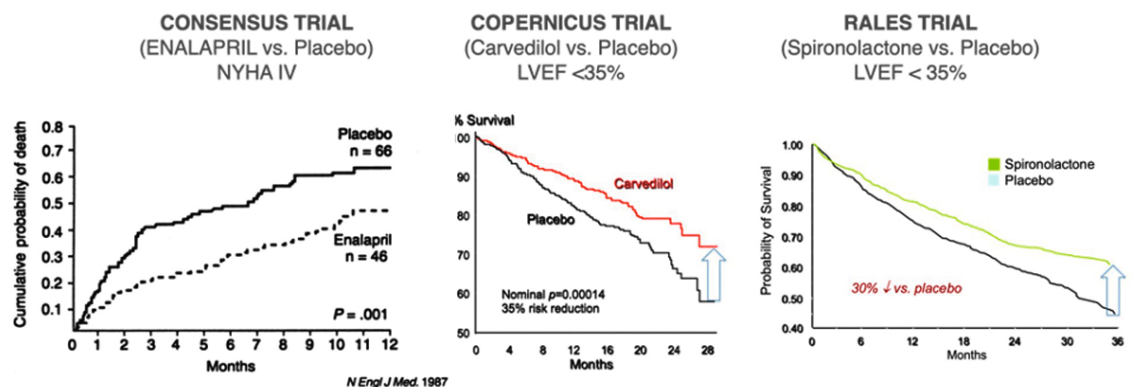
It all changed with the CONSENSUS Trial, which showed, for the first time, that in severe heart failure an angiotensin converting enzyme (ACE) inhibitor, such as enalapril improved the overall status of patients, their symptoms, hospital stay and mortality [4]. However, patients still eventually died of heart failure [5], and the treatment appeared palliative in nature. ACE inhibition therefore was followed by beta-blockers, which were shown to be effective in addition to enalapril, captopril or any ACE inhibitor and further improved outcomes of patients with pump failure. As a result, bisoprolol, carvedilol and metoprolol entered clinical

routine swiftly [6–8]. The third drug class that followed and again improved outcomes were mineralocorticoid receptor antagonists, such as spironolactone [9] and later also eplerenone (fig. 1) [10].

These seminal trials, including the more recent PARADIGM trial [11], were all performed in patients with a left ventricular ejection fraction (LVEF) of less than 40%, or even less than 35%, as trialists wanted to see events in order to obtain enough statistical power to prove efficacy of the drugs tested, compared with placebo or standard therapy of that time. As such, heart failure with reduced ejection fraction or HFrEF was born and appeared in the 2016 ESC Guidelines on the Diagnosis and Treatment of Acute and Chronic Heart Failure. Of note, there was no specific pathophysiological reason to select a limit of 40% or less, but it made its way into trials and the guidelines until this day [2].

The 2016 ESC Guidelines on the Diagnosis and Treatment of Acute and Chronic Heart Failure [12] also introduced a new category called HFmrEF or heart failure with mid-range ejection fraction. Indeed, although for the lay person this tongue twister seemed just a milder form of HFrEF, for clinical scientists it was a no-man's land, as hardly any trial had documented the effectiveness of any drug in this patient population with a LVEF of 40–50%. Then a sub-analysis of the *TopCat* Trial quite convincingly demonstrated that spironolactone tended to be effective in reducing major cardiovascular events (MACE) in patients with heart failure as the ejection fraction tended to get lower than 50% [13]. This was further confirmed in the PARAGON Trial, using sacubitril/valsartan in this patient

Figure 1 : The first seminal trials in heart failure demonstrating the clinical effectiveness on outcomes in patients with heart failure with reduced ejection fraction HFrEF (modified from [4, 7, 9]). NYHA = New York Heart association; LVEF = left ventricular ejection fraction



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group. As a consequence the 2021 ESC Guidelines on the Diagnosis and Treatment of Acute and Chronic Heart Failure, renamed HFmrEF as heart failure with mildly reduced ejection fraction, as this group of patients responded to a standard drug regimen very similarly to patients with HFrEF – essentially HFmrEF and HFrEF are the same condition, just with different degrees of severity (table 1) [2].

The surprising diabetic drugs

In the search of novel antidiabetic drugs, it turned out that molecules interfering with the sodium-glucose type 2 transporter (SGLT2) in the kidney not only improved glucose control to some extent, but, most importantly, for the first time reduced mortality in patients with type 2 diabetes [14]. Sub-analyses showed that a secondary endpoint, hospitalisation for heart failure, was also markedly reduced. This eventually led to seminal trials with empagliflozin [15] and dapagliflozin [16] in patients with HFrEF, which showed impressive effects of hospitalisations for heart failure and in part on mortality. Therefore, the 2021 ESC Guidelines on the Diagnosis and Treatment of Acute and Chronic Heart Failure added a forth pillar to the management of patients with heart failure (fig. 2) [2].

What is HFpEF?

The remainder of patients who have symptoms of heart failure, such as fatigue, breathlessness and oedema, and hospitalisations for these symptoms, but have a LVEF >50% with much milder increases in natriuretic peptides, have, as a consequence, been lumped together into a third category, HFpEF or heart failure with preserved ejection fraction. However, whether this group of patients is really a homogenous entity is quite doubtful.

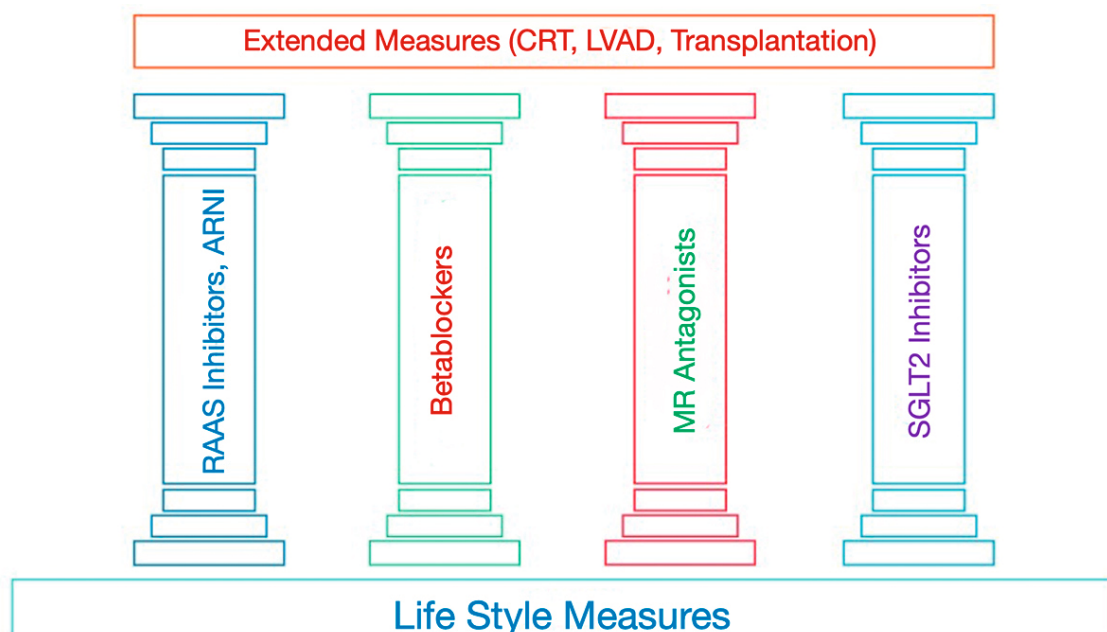
Large registries have shown that the sweet spot of LVEF for survival is actually 60%, and below and above mortality steadily increases, particularly in the former, and less so in the latter (fig. 3) [17]. Based on these findings, patients with an ejection fraction of 50–60% should probably be renamed heart failure with very mildly (rather than mildly) reduced ejection fraction, but not HFpEF. Indeed, patients with cardiomyopathies, probably less so in ischaemic heart failure, with LVEF in this range may already have an increased risk of fatal arrhythmias and future pump failure, depending on the genetic cause of their condition.

As a side remark: the definitions of heart failure categories assume a precision and reproducibility of LVEF measurements with echocardiography (the most widely used diagnostic tool) that is far from reality. Indeed, the reproducibility of LVEF with echocardiography has a variation

Table 1: : Categorisation of heart failure according to the 2021 ESC Guidelines on the Diagnosis and Treatment of Acute and Chronic Heart Failure [2]. HFrEF = heart failure with reduced ejection fraction; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction (modified from [2])

Type of HF	HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs ^a	Symptoms ± Signs ^a
	2	LVEF ≤40%	LVEF 41–49% ^b
	3	—	—
			Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides ^c

Figure 2: : The four pillars of the management of patients with heart failure with reduced ejection fraction (HFrEF). ARNI = angiotensin receptor-neprilysin inhibitor; CRT = cardiac resynchronisation therapy; LVAD = left ventricular assist device; MR = mineralocorticoid receptor; RAAS = renin-aldosterone-angiotensin system; SGLT2 = sodium-glucose type 2 transporter



of up to 10%, making such precise categorisation a bit theoretical.

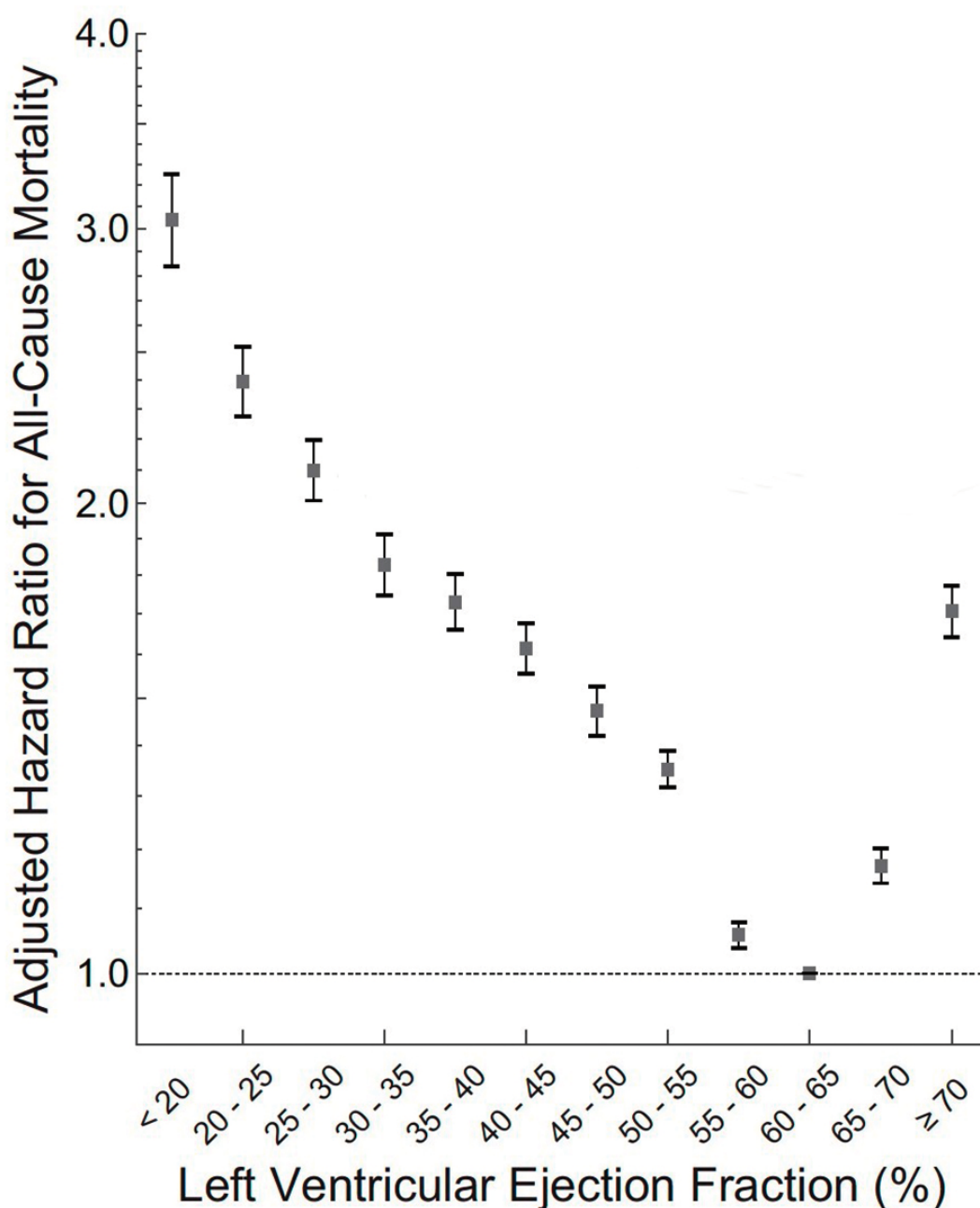
Furthermore, patients with elevated LVEF >65%, such as those with hypertrophic cardiomyopathy, hypertensive heart disease, or just small and stiff left ventricles and large atria associated with dyspnoea, or decreased exercise tolerance are a heterogeneous group. Whereas patients with hypertrophic cardiomyopathy have specific mutations of contractile proteins and thus can be well characterised and their level of risk assessed [18], patients with hypertensive heart disease have left ventricular remodelling and hypertrophy [19], decreased left ventricular compliance and increased filling pressures and, in turn, may experience symptoms of heart failure, and the last group may just have

an aged heart. Finally, patients with transthyretin (TTR) amyloid heart disease initially have normal LVEF, but very stiff hearts due to the deposition of the misfolded amyloid protein, and are amenable now to a specific treatment such as tafamidis [20] or an antisense oligonucleotide [21]. A remaining question is whether some patients with symptoms of heart failure and normal LVEF are just obese and deconditioned.

EMPEROR Preserved: an important step forward

At the European Society of Cardiology Annual Meeting in late August 2021, the seminal EMPEROR Preserved Trial

Figure 3: Relation between left ventricular ejection fraction as assessed by echocardiography in 203,135 Individuals related to mortality (modified from [17]).



was presented. This enrolled patients with a median age of around 70 years and an LVEF above 40%, symptoms of heart failure, as well as N-terminal pro-B-type natriuretic peptide (NTproBNP) levels of >300 pg/ml for those in sinus rhythm or of >900 pg/ml for those in atrial fibrillation. Patients were randomised to empagliflozin 10 mg once daily or placebo on top of current standard guideline recommended therapy. Amazingly, the trial was positive, unlike PARAGON with sacubitril/valsartan. Of note, the effect size with a hazard ratio of 0.21 on a placebo event rate of 10% at one year was driven by heart failure hospitalisations and not mortality (fig. 4) [22].

In the media this finding was clearly seen as a breakthrough in patients with HFpEF. However, is this interpretation strictly correct? Overall there was no interaction between LVEF and outcomes. However, the sub-group analysis of the trial clearly showed that the most dominant effect was seen in patients with LVEF between 40 and 50%, i.e. in patients with HFmrEF rather than HFpEF, a borderline effect within a confidence interval of 0.64–0.99 in those with a LVEF of $\geq 50\%$ to $\geq 60\%$ and no effect in those with a LVEF $>60\%$ (fig. 5; [22]). Of note, the effect size, very much as in PARAGON, tended to be somewhat

larger in females than in males, as well as in the elderly compared with those <70 years of age.

Modern heart failure management

Thus, EMPEROR Preserve is a seminal trial; it expands the effectiveness of drugs proven to reduce heart failure hospitalisations in HFrfEF to HFmrEF and in part to those with an LVEF between ≥ 50 to $<60\%$. Thus, for patients in these categories, empagliflozin should be considered if symptoms of heart failure are present and NTproBNP is >300 pg/ml in those in sinus rhythm and >900 pg/ml in those with atrial fibrillation. The particularly good effect in the elderly shows that such treatment should not be withheld because of the age of the patient.

However, in patients with elevated LVEF and symptoms of heart failure and moderately elevated NT-proBNP, hypertrophic or hypertensive cardiomyopathy or even TTR amyloid heart disease should be excluded and treated according to guidelines.

Potential competing interests

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Figure 4: Results of the EMPEROR Preserved trial with Kaplan-Meier curves of the primary outcome (left) and heart failure hospitalisations (right; modified from [22]).

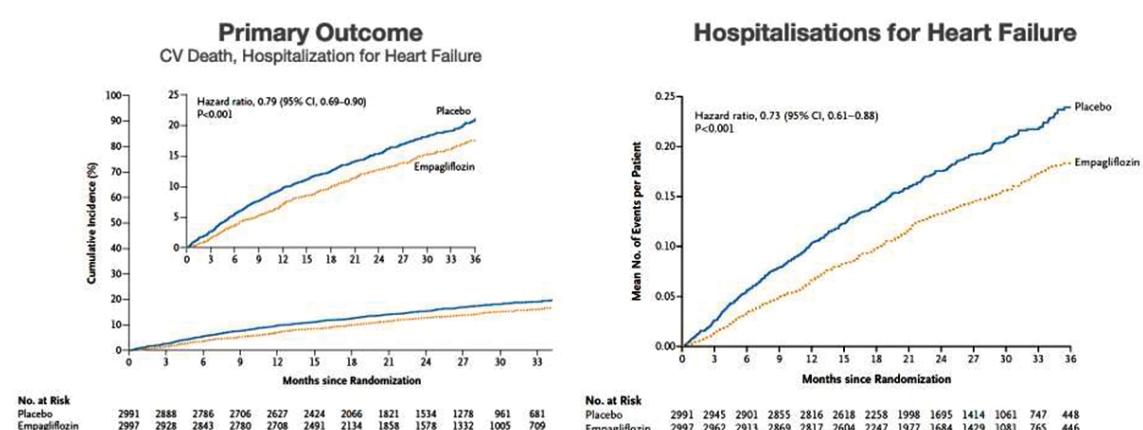


Figure 5: Subanalysis of the EMPEROR preserved trial in predefined subgroups (modified from [22]). CI = confidence interval; LVEF = left ventricular ejection fraction

Subgroup	Empagliflozin no. of patients with events/total no.	Placebo no. of patients with events/total no.	Hazard Ratio (95% CI)
Overall	415/2997	511/2991	0.79 (0.69–0.90)
Diabetes at baseline			
Yes	239/1466	291/1472	0.79 (0.67–0.94)
No	176/1531	220/1519	0.78 (0.64–0.95)
LVEF at baseline			
<50%	145/995	193/988	0.71 (0.57–0.88)
$\geq 50\%$ to $<60\%$	138/1028	173/1030	0.80 (0.64–0.99)
$\geq 60\%$	132/974	145/973	0.87 (0.69–1.10)
Age			
<70 yr	134/1066	152/1084	0.88 (0.70–1.11)
≥ 70 yr	281/1931	359/1907	0.75 (0.64–0.87)
Sex			
Male	253/1659	297/1653	0.81 (0.69–0.96)
Female	162/1338	214/1338	0.75 (0.61–0.92)

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