Reconsidering the ejection fraction centric view of pharmacologic treatment for heart failure.

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Abstract

For the past two decades, heart failure (HF) has been classified into two phenotypes based on ejection fraction (EF). Inhibitors of the RAAS, neprilysin, , and beta-blockers represent foundational treatments for patients with a reduced EF (<40%) but have not been considered effective in patients with preserved EF (≥40%). However, re-examination of the clinical trial evidence has cast considerable doubt about the utility of an EF threshold of 40% as the main decision tool for HF treatment. In CHARM, candesartan reduced the risk of cardiovascular death or HF hospitalization by 24% up to an EF of 50%, with attenuation of the effect on HF hospitalization in patients with EF >55-60%. In RALES and TOPCAT, spironolactone reduced the risk of cardiovascular death or HF hospitalization by 28% up to an EF of 50%, with attenuation of the effect on HF hospitalization in patients with EF >55-60%. In PARADIGM-HF and PARAGON-HF, sacubitril/valsartan reduced total HF hospitalizations by 20% up to an EF of 55-60%, with an attenuated effect in patients with the highest EF. In the EMPEROR trials, empagliflozin reduced the risk of total HF hospitalizations by approximately 30% in patients with EF ranging from <25% to 60%, with an attenuated effect in patients with EF >60-65%. Since patients with an EF >60% represent only 10-15% of all HF patients, we propose that foundational HF treatments should be applied to patients across broad range of EF.

Key-words: ejection fraction; heart failure; unified definition.

Introduction

In 1628 William Harvey described in detail the mechanisms of the circulatory system, with the heart playing a central role by pumping the blood throughout the entire body while emptying completely during systole.[1] Later in the 19th century some authors observed that some blood remained in the heart after its contraction,[2,3] and in 1906 Yandell Henderson estimated that approximately 2/3 of total volume of the left ventricle would be discharged during systole.[4] Two decades later, Gustav Nylin proposed that the relation between heart volume and cardiac output per beat (i.e., stroke volume) could be used as a measure of cardiac activity.[5]

Since the early 20th century, heart failure (HF) has been defined as "a condition in which the heart fails to discharge its contents adequately", [6] and in 1962, Folse and Braunwald showed that the ratio of stroke volume (SV) divided by the end-diastolic volume (EDV) of the left ventriculus could provide relevant information to a hemodynamic analysis of left ventricular function.[7] A few years later Stuart Bartle proposed the term "ejected fraction" to reflect the ratio of SV to EDV.[8] As it became clear that the HF syndrome was accompanied by elevated cardiac filling pressures along with a reduced proportion of ejected left ventricular volume, LVEF became a convenient means to examine ventricular function, despite the fact that it is principally a crude measure of left ventricular volume that is preload and afterload dependent.[9] The ratio of SV to EDV is not a measure of myocardial contractility; changes in the ratio do not reflect changes in the degree of myocardial shortening; and measurements relating to the myocardium are not included in determination of the LVEF.[10,11] Furthermore, LVEF assessment may have poor reproducibility

depending on the observer and the used method.[12,13] Nonetheless, despite its major limitations and only moderate reproducibility, the ready availability of LVEF led it to become the leading metric used by clinicians to characterize the left ventricular function of their patients.

Use of ejection fraction in heart failure trials

In the 1980s randomized, controlled, and double-blind trials (RCTs) in HF started to be conducted.[14] The first large RCT with a survival endpoint, the Veterans Administration Cooperative Study (V-HeFT-I),[15] selected patients taking digoxin and a diuretic to receive additional double-blind treatment with placebo, prazosin, or the combination of hydralazine and isosorbide dinitrate based on evidence of cardiac dilatation (cardiothoracic ratio >0.55 on chest x-ray or a left ventricular internal diameter in diastole >2.7 cm/m^2 on echocardiography) or a radionuclide ejection fraction <45% in association with reduced exercise tolerance. The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) trial randomized patients to enalapril or placebo based on the presence of severe symptoms and a radiologically-determined heart size >600 ml/m^2 in men and >550 ml/m^2 in women, without the characterization of ejection fraction.[16]

However, in the late 1980s and 1990s, LVEF became a systematic inclusion criterion in HF trials. The Studies of Left Ventricular Dysfunction (SOLVD),[17] the Assessment Trial of Lisinopril and Survival Trial (ATLAS),[18] the Prospective Randomized Amlodipine Survival Evaluation Study Group (PRAISE),[19] the Flolan International Randomized Survival Trial (FIRST),[20] the U.S. Carvedilol Heart Failure Study,[21] and the Randomized Aldactone Evaluation Study (RALES)[22] trials required patients to

have a LVEF ≤25-35%. The use of LVEF as an inclusion criterion in HF trials continued thereafter.[23-25]

Classification of heart failure based on ejection fraction

Hemodynamic studies found that some patients had elevated filling pressures without marked increases in ventricular chamber size, and such patients were initially termed “diastolic HF”.[26] Clinically, these patients did not differ from those with systolic dysfunction, and in most such patients, myocardial shortening was impaired, often markedly so.[11] The distinguishing feature of these patients was that the depression of contractility was not accompanied by marked left ventricular enlargement, in contrast with those whose ejection fraction were demonstrably low.[11]

Evidence on how to treat patients with heart failure without a reduced ejection fraction was lacking, because most trials enrolled patients with marked left ventricular enlargement or a severely reduced ejection fraction.[27] One exception is the Digitalis Investigation Group (DIG) trial, whose ancillary trial enrolled 988 patients (492 assigned to digoxin and 496 assigned to placebo) with a LVEF >45%. The results of this ancillary study were consistent with the findings of the main trial, with a HR of 0.99, 95%CI 0.76 to 1.28) for all-cause mortality and a HR of 0.82, 95%CI, 0.63 to 1.07 for the composite of all-cause death or hospitalization for HF.[28] Subsequently, the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program included HF patients with both an ejection fraction less than and greater than 40%. The CHARM-Preserved trial included patients with a LVEF ≥40% and HF symptoms to compare candesartan (an angiotensin receptor blocker, ARB) with placebo.[29] The trial investigators proposed

to identify a group of patients who had been excluded in prior trials, thus addressing a therapeutic void rather than making a mechanistic distinction. After the publication of CHARM-Preserved, the use of the term “preserved HF or HFpEF” for patients with an ejection fraction ≥40% became widely adopted, and it continues to be used at the present time.[30]

Some further subclassification of HFpEF has evolved over the years. The most popular one is the “mid-range ejection fraction or HFmrEF or mildly reduced ejection fraction” used to characterize patients with LVEF of 41% to 49%.[31-33]

Most HF treatments are recommended to patients with a LVEF <40%.[34,35] Of course, people who take the guidelines literally may not treat a patient in whom they measured a LVEF of 43% while another colleague could have measured 39% in the same patient on the same day.[36] Moreover, patients with a LVEF ≥40% or >50% typically have myocardial contractile “systolic” impairment of the left ventricle when measured by other assessments (e.g., strain analysis or myocardial contraction fraction).[10,11,37-39]

Interpretation of large RCT in heart failure with preserved ejection fraction

Several landmark RCTs have provided robust evidence that angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), beta-blockers, mineralocorticoid receptor antagonists (MRAs), sacubitril/valsartan, and the sodium glucose co-transporter 2 inhibitors (SGLT2i) dapagliflozin and empagliflozin significantly improve mortality and morbidity in patients with a LVEF <40%.[34,35,40-42] Most of these treatments have also been tested in patients with a LVEF ≥40% or

>45% but, in most cases, with less compelling results when compared with patients with a LVEF <40%.

Angiotensin converting enzyme inhibitors

Perindopril

In the PEP-CHF study, a total of 850 patients aged ≥70 years with a clinical and echocardiographic diagnosis of predominantly mild to moderate HF due to diastolic dysfunction on echocardiography were randomized to either perindopril 4 mg or placebo.[43] Patients with a left ventricular wall motion index of <1.4 (a proxy for HFrEF) were excluded. Many patients withdrew from perindopril (28%) and placebo (26%) after the first year of follow-up and started taking open-label ACEi. At the end of follow-up (median 2.1 years), the composite endpoint of all-cause mortality and HF hospitalization did not differ between groups: HR 0.92, 95%CI 0.70-1.21, P =0.55. However, at 1 year, when most patients were still taking the assigned treatment, perindopril appeared to improve symptoms and exercise tolerance, and reduced HF hospitalizations: HR 0.63, 95%CI 0.41-0.97, P =0.033.

Angiotensin receptor blockers

Candesartan

In the CHARM program, patients with LVEF>40% were allocated to the CHARM-Preserved trial, [29] which included 3023 patients (65% of the patients had a LVEF≥50% and 35% a LVEF >40 and <50%). Compared with placebo, candesartan did not reduce the risk of the primary outcome, a composite of time-to-first of cardiovascular death or HF hospitalization; unadjusted HR 0.86, 95%CI 0.77-1.03, P =0.12. In the prespecified covariate adjusted analysis the hazard ratio was 0.86,

95%CI 0.74-1.00, P =0.051. Fewer patients were hospitalized for HF in the candesartan group (230 vs. 279, P =0.017). Together, these findings support a statistically significant and clinically meaningful effect of candesartan for preventing HF admissions among patients who have HF and a LVEF >40%.[29]

Analyzing the effect of candesartan across the continuous spectrum of LVEF showed that the drug reduced the time-to-first cardiovascular death or HF hospitalization by 24% up to a LVEF of 50%, with attenuation of the effect on heart failure hospitalization in patients with EF of 60% or greater.[39] Candesartan did not reduce cardiovascular mortality in these patients.[44]

Irbesartan

The Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial tested irbesartan vs. placebo in 4133 patients with a LVEF≥45% who were aged 60 or older.[45] Irbesartan did not reduce the primary outcome of all-cause mortality or hospitalizations for cardiovascular causes (HR 0.95, 95%CI 0.86-1.05, P =0.35 or HF hospitalizations HR 0.95, 95%CI 0.81-1.10, P =0.50). However, a post-hoc analysis adjusting for baseline variables with prognostic impact, suggested benefit with irbesartan treatment with a 13% reduction in the time-to-first of cardiovascular death or HF hospitalization: HR 0.87, 95%CI 0.77-0.99, p=0.039.[46]. Ejection fraction (<60% vs. ≥60%) did not modify the effect of irbesartan on the primary outcome, interaction P =0.28.[45]

Beta-Blockers

The Beta-blockers in Heart Failure Collaborative Group pooled individual patient-level data from double-blind RCTs in HF in order to examine the effects of beta-blockers across the spectrum of LVEF.[47] Among 14262 patients in sinus rhythm, beta-blockers improved outcomes among patients with a LVEF up to 50%. It should be noted that only 241 patients had a LVEF >50%, all from the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS) trial;[48] hence, this subgroup is too small to form the basis of valid conclusions. However, most patients with HFpEF are already receiving beta-blockers, presumably for other cardiovascular disorders.

Spironolactone

The Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial investigated the prognostic effect of spironolactone vs. placebo in 3,445 patients with a LVEF≥45% randomized in North America, South America and Canada i.e., “the Americas” and Russia/Georgia i.e., “Eastern Europe”.[49] The primary outcome was a composite endpoint of cardiovascular death or HF hospitalization. Spironolactone did not reduce the primary outcome, HR 0.89, 95%CI 0.77-1.04, P =0.14 but did reduce HF hospitalizations: HR 0.83, 95%CI 0.69-0.99, P =0.04. However, marked regional variations were seen in the trial, whereby patients from Eastern Europe had event rates similar to the general population of those countries, raising the likelihood that these patients did not have heart failure. Furthermore, these patients did not experience rises in serum potassium and creatinine with spironolactone; and the analysis of blood spironolactone metabolites confirmed a low treatment adherence in Eastern Europe.[50,51] When the analysis excluded patients from Eastern Europe, spironolactone reduced the primary

outcome (HR 0.82, 95%CI 0.69-0.98, P =0.026). Further analysis suggested that ejection fraction influenced the magnitude of the effect of spironolactone, with an attenuated effect in patients with an ejection fraction >55-60%.[52]

Sacubitril/Valsartan

The Efficacy and Safety of LCZ696 Compared to Valsartan on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction trial (PARAGON-HF) trial examined the efficacy and safety of sacubitril/valsartan vs. valsartan in 4822 patients aged 50 years or older with LVEF ≥45%, structural heart disease, and increased levels of natriuretic peptides. The primary outcome was a composite of total hospitalizations for HF or cardiovascular mortality.[53] Compared with valsartan, sacubitril/valsartan exerted a modest effect to reduce the rate of the primary outcome: RR 0.87, 95%CI 0.75-1.01, P =0.06. Subgroup analyses showed that patients with LVEF below the median (of 57%) and women had a greater benefit with sacubitril/valsartan.[54-56] Additionally, sacubitril/valsartan led to significant improvements in quality-of-life scores and NYHA class, as well as lower rates of renal events and worsening renal function.[57] Analyses across the continuous spectrum of LVEF showed that sacubitril/valsartan (vs. valsartan) reduced first and recurrent HF hospitalizations up to a LVEF of 55-60%, with an attenuated effect in patients with an ejection fraction of 60% or greater.[55]

Sodium-glucose cotransporter 2 inhibitors

The Empagliflozin Outcome trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction (EMPEROR-Preserved) trial enrolled patients with HF and a LVEF >40%. Compared with placebo, empagliflozin reduced the composite of

cardiovascular death or heart failure hospitalizations by 21% (HR 0.79, 95%CI 0.69-0.90, P <0.001) and recurrent HF hospitalizations by 27% (HR 0.73, 95%CI 0.61-0.88, P <0.001) with no treatment effect modification by LVEF for the primary outcome.[58] However, the effect of empagliflozin on heart failure hospitalizations became attenuated at an ejection fraction of >60%.[59]

The challenges in the interpretation of HFpEF trials are displayed in *Table 1*, and the LVEF subgroup analysis of HFpEF trials displayed in *Table 2*.

Totality of evidence

As above stated, ejection fraction reflects the volume rather than the contractility of the heart. Based on the available evidence, most drugs used for the treatment of patients with heart failure (inhibitors of the renin-angiotensin system, sacubitril/valsartan, MRAs and SGLT2i) appears to be beneficial in reducing heart failure hospitalizations across a broad spectrum of ejection fractions, at least, up to 55-60%. Additionally, these drugs reduce cardiovascular mortality in patients with an ejection fraction of 40% or less.

The pathophysiology of patients with heart failure who have an ejection fraction of 60% or greater requires further study. These patients represent one-third of those with HFpEF but only 10-15% of all patients included in heart failure trials and are represented mostly by women with atrial fibrillation (who may require specific treatments for atrial fibrillation). Therefore, we propose that foundational HF treatments should be applied to patients across broad range of EF.

Disclosures

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Table 1. Main results of HFpEF trials

Trial	LVEF range	Interpretation issues	Re-analysis	Re-interpretation
PEF-CHF (Perindopril vs. Placebo)	LVEF was not used for inclusion	High rates of open-label ACEi after 1 year	1-year analysis	Perindopril reduced HF hospitalizations and improved HF symptoms
CHARM-Preserved (Candesartan vs. Placebo)	54±9%	Total HFH not considered	Total (first and recurrent) HFH	Candesartan reduced first and recurrent HFH with an attenuation of effect at LVEF >60%
I-Preserve (Irbesartan vs. Placebo)	60±9%	Adjustment for prognostically important variables not considered	Covariate adjusted	Irbesartan reduced the composite of HFH or CV death
Beta-blockers in Heart Failure Collaborative Group (Beta-blockers vs. Placebo meta-analysis)	Most (n =575) patients with LVEF 40-49%	Only 241 patients with LVEF ≥50% (all from the SENIORS trial)	Across LVEF range	Beta-blockers improved prognosis up to LVEF of 50% in sinus rhythm, but underpowered above 50%.
TOPCAT (Spironolactone vs. Placebo)	56 (51-61)	Marked regional differences with HF diagnosis and adherence issues detected in Eastern Europe	Regional analysis	Spironolactone improved outcomes in patients enrolled in the Americas but not in Eastern Europe The effect of spironolactone was attenuated at LVEF >60%
PARAGON-HF (Sacubitril/Valsartan vs. Valsartan)	58±8%	Treatment effect more pronounced in women and LVEF below the median of 57%	Sex differences and LVEF spectrum	Sacubitril/Valsartan improved outcomes in women and in patients with LVEF below 60% The effect of sacubitril/valsartan was attenuated

				at LVEF >60%
EMPEROR-Preserved (Empagliflozin vs. Placebo)	54±9%	None	Spectrum of ejection fraction	Empagliflozin improved outcomes The effect of empagliflozin to reduce HF hospitalizations was attenuated at LVEF >60-65%

Legend: LVEF, left ventricular ejection fraction; HFH, heart failure hospitalization.

Table 2. Treatment effect on the primary endpoint of heart failure hospitalization and cardiovascular death, across the spectrum of ejection fraction

Outcome/Drug/Trial	**LVEF <40%**	**LVEF 40-49%**	**LVEF 50-60%**	**LVEF >60%**
Candesartan vs. Placebo *				
CV death or HFH	0.82 (0.75–0.91)	0.76 (0.61–0.96)	0.95 (0.79–1.14)	-
Total HFH	0.68 (0.58–0.80)	0.48 (0.33–0.70)	0.78 (0.59–1.03)	-
Sacubitril/Valsartan vs. Active comparator **				
CV death or HFH ***	0.81 (0.69-0.94)	0.89 (0.73-1.10)	0.89 (0.74-1.06)	1.03 (0.80-1.32)
Total HFH ***	0.82 (0.63-1.06)	0.77 (0.58-1.02)	0.81 (0.63-1.05)	1.04 (0.76-1.44)
Spironolactone vs. Placebo ****				
CV death or HFH	0.69 (0.58-0.82)	0.72 (0.50-1.05)	0.85 (0.61-1.18)	0.97 (0.76-1.23)
First HFH	0.65 (0.54-0.77)	0.76 (0.46-1.27)	0.70 (0.47-1.04)	0.98 (0.74-1.30)
Beta-blockers vs. Placebo *****				
CV death or CV hosp.	0.74 (0.62–0.88)	0.83 (0.60–1.13)	0.66 (0.38–1.15)	-
Empagliflozin vs. Placebo ******				
CV death or HFH	0.75 (0.65-0.86)	0.71 (0.57-0.88)	0.80 (0.64-0.99)	0.87 (0.69-1.10)
Total HFH	0.70 (0.58-0.85)	0.57 (0.42-0.79)	0.66 (0.48-0.91)	1.07 (0.76-1.46)

Legend: LVEF, left ventricular ejection fraction; HFH, heart failure hospitalization; Inter.P, interaction P-value.

* The treatment effect represented for patients with a LVEF between 50 and 60%, represents the effect in the subgroup of patients with LVEF ≥50%; The effect of candesartan vs. placebo across the continuous spectrum of LVEF is represented with “splines” with imprecise results at LVEF >60% due to a small number of patients/events (*Lund L et al. European Journal of Heart Failure 2018; 20, 1230–1239).*

** The “active comparator” was enalapril in PARADIGM-HF (*McMurray JJV et al. N Engl J Med 2014; 371:993-1004*) and valsartan in PARAGON-HF (*Solomon SD et al. N Engl J Med 2019; 381:1609-1620*).

*** In PARAGON-HF the represented cutoffs are: 32.5-42.5%, 42.6-52.5%, 52.6-62.5%, and >62.5% (*Solomon SD et al. Circulation 2020; 5, 352–361).*

**** The effect of spironolactone vs. placebo in the subgroup of patients with a LVEF <40% is taken from the RALES trial where the composite of CV death or HFH represents CV death alone (*Pitt B et al. N Engl J Med 1999; 341:709-717*); TOPCAT included patients with LVEF ≥45% hence the subgroup of patients with a LVEF 40-

49% is instead 45-49% and the subgroup with LVEF ≥50% is instead 50 to 55%; The interaction P is for the TOPCAT trial subgroups (*Solomon SD et al. European Heart Journal 2016; 37, 455–462)*.

***** Results taken from *Cleland JGF et al. European Heart Journal 2018: 39, 26-35*; The results are presented for patients in sinus rhythm at baseline; All patients with LVEF >50% (n =241) came from the SENIORS trial (*Flather MD et al. European Heart Journal 2005; 26, 215-25*).

****** Results taken from the EMPEROR-Reduced (*Packer M et al. N Engl J Med 2020; 383:1413-1424*) and EMPEROR-Preserved (*Anker SD et al. NEJM; 385:1451-1461and Packer M et al. Circulation 2021 in press*) trials; The interaction is for the EMPEROR-Preserved trial (*Anker SD et al. NEJM 2021 in press and Packer M et al. Circulation 2021; 144:1284–1294*).