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# The four pillars of HFrEF therapy: is it time to treat heart failure regardless of ejection fraction?

**Kieran F. Docherty[1], Antoni Bayes-Genis[2], Javed Butler[3,4], Andrew J.S. Coats[5], Mark H. Drazner[6], Emer Joyce[7,8], and Carolyn S.P. Lam[9]***

*[1]British Heart Foundation Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, 126 University Place, Glasgow G12 8TA, UK; [2]Institut del Cor, Hospital Universitari Germans Trias i Pujol, CIBERCV, 08916 Badalona, Barcelona, Spain; [3]Baylor Scott and White Research Institute, 3434 Live Oak St Ste 501, Dallas, TX 75204, USA; [4]Department of Medicine, University of Mississippi Medical Center, 2500 N State St, Jackson, MS 39216, USA; [5]Warwick Medical School, University of Warwick, Coventry, CV4 7HL, UK; [6]University of Texas Southwestern Medical Center, Department of Internal Medicine, Division of Cardiology, 5323 Harry Hines Blvd., Dallas, TX 75390-9254, USA; [7]Department of Cardiology, Mater Misericordiae University Hospital, Eccles St, Dublin 7, D07 R2WY, Ireland; [8]School of Medicine, University College Dublin, Bellfield, Dublin 4, Ireland; and [9]National Heart Centre Singapore, Duke-National University of Singapore, 5 Hospital Dr, Singapore 169609, Singapore*

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The syndrome of heart failure (HF) has historically been dichotomized based on clinical trial inclusion criteria into patients with a reduced or preserved left ventricular ejection fraction (LVEF) using a cut-off of above or below 40%. The majority of trial evidence for the benefits of disease-modifying pharmacological therapy has been in patients with HF with reduced ejection fraction (HFrEF), i.e. those with an LVEF ≤40%. Recently, the sodium-glucose co-transporter 2 inhibitors empagliflozin and dapagliflozin have been shown to be the first drugs to improve outcomes in HF across the full spectrum of LVEF. There is, however, growing evidence that the benefits of many of the neurohumoral modulators shown to be beneficial in patients with HFrEF may extend to those with a higher LVEF above 40% but still below the normal range, i.e. HF with mildly reduced ejection fraction (HFmrEF). Whether the benefits of some of these medications also extend to patients with HF and preserved ejection fraction (HFpEF) is an area of ongoing debate. This article will review the evidence for HF treatments across the full spectrum of LVEF, provide an overview of recently updated clinical practice guidelines, and address the question whether it may now be time to treat HF with some therapies regardless of ejection fraction.

## Introduction

The signs and symptoms of heart failure (HF) are secondary to elevated cardiac filling pressures. In a proportion of patients, the syndrome of HF occurs in the setting of a reduced left ventricular ejection fraction (LVEF).[1] A reduction in LVEF is invariably accompanied by ventricular dilatation; indeed, the degree of reduction in LVEF strongly correlates with the degree of ventricular dilatation. LVEF is also highly dependent on loading conditions, whether that be the afterload or preload. In addition to loading conditions, the LVEF is influenced by the modality used to assess it, as well as by significant interobserver and test–retest variability.[2] The degree of LVEF impairment and ventricular dilatation, and the extent of improvement in LVEF and ventricular volumes with treatment, are powerful predictors of outcome in patients with HF.[3–5] In some patients, however, elevated cardiac filling pressures (and signs and symptoms of HF) are present without a frank reduction in

*Corresponding author. Tel: +65 67048965, Fax: +65 68449069, Email: carolyn.lam@duke-nus.edu.sg

the LVEF. These patients without significant ventricular dilatation frequently have reduced longitudinal systolic contractility, often with compensatory increases in circumferential contraction, thereby 'preserving' the LVEF.[6] Approximately one half of patients with clinical HF have an LVEF which is not markedly reduced, highlighting the heterogeneous nature of this syndrome.[7]

Despite its shortcomings, LVEF has become the key metric in decision-making regarding the treatment of patients with HF. In the 1980s, many of the first large-scale randomized clinical trials in HF did not specify specific inclusion criteria by LVEF, rather mandating the presence of ventricular dilatation as a surrogate of a depressed LVEF.[8] The first large trial to mandate inclusion based on an LVEF threshold (≤35%) was the Studies of Left Ventricular Dysfunction (SOLVD) programme and in the following years, both clinical trials and international treatment guidelines used a cut-off of ≤35–40% to denote a group of patients with HF with reduced ejection fraction (HFrEF).[9-11] It is this group in whom the majority of evidence of treatment benefit from pharmacological and device therapy has been established. The Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) programme, in a recognition that not all patients with HF have a frankly reduced LVEF, was the first trial to examine the potential benefits of the angiotensin type-1 receptor inhibitor candesartan in patients with an LVEF >40%, a group referred to by the CHARM-Preserved investigators as having HF with preserved ejection fraction (HFpEF).[12] Subsequently, the arbitrary cut-offs of 40 or 45% were used to dichotomize patients into the phenotypes of HFrEF or HFpEF. A series of trials with the neurohumoral modulators known to be beneficial in HFrEF failed to demonstrate efficacy in HFpEF.[12-16] Indeed, it is only within the last year that the first trial has been published reporting a significant morbidity and mortality benefit of a pharmacological treatment [the sodium-glucose co-transporter 2 inhibitor (SGLT2i) empagliflozin] in HF patients with LVEF >40%, the results of which have since been replicated with another agent in this drug class (dapagliflozin).[17,18]

Recent *post-hoc* analyses of clinical trial data have shown that the benefits of many of the therapies demonstrated to be beneficial in patients with HFrEF may extend to those with an LVEF threshold above 40%, including those with HF and mildly reduced ejection fraction (HFmrEF) as defined by an LVEF between 41 and 49%.[19-23] Contemporary international guidelines for the management of HF, and a recently proposed Universal Definition of HF, have classified patients as having HFrEF (LVEF ≤40%), HFmrEF (LVEF 41–49%), or HFpEF (LVEF ≥50%), and provided treatment recommendations for each of these groups.[10,11,24] With regards to HFrEF, based on a wealth of evidence, the AHA/ACC/HFSA and ESC heart failure guidelines now advocate for the use of five medications in four tablets, a combination frequently referred to as the 'four foundational pillars' of treatment for HFrEF: the combination of a neprilysin inhibitor and an angiotensin receptor blocker (ARB) in the form of sacubitril/valsartan, a beta-blocker, a mineralocorticoid receptor antagonist (MRA), and an SGLT2i.[10,11] This article will review the evidence to extend the use of these therapies from patients with HFrEF to those with higher ejection fractions, and address the question whether it may now be time to treat HF regardless of ejection fraction.

## The four pillars of heart failure therapy

### Renin-angiotensin inhibitors alone or in combination with a neprilysin inhibitor

#### Evidence in HFrEF

Activation of the renin angiotensin system (RAS) is a pathophysiological hallmark of HF and is a key driver of the development and progressive worsening of HFrEF. The benefits of pharmacological inhibition of the RAS were first demonstrated in the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) in patients with New York Heart Association (NYHA) IV symptoms; the angiotensin-converting enzyme (ACE) inhibitor enalapril (target dose of 20 mg twice daily), compared with placebo, substantially reduced the risk of mortality by 40% at 6 months.[8] In the SOLVD-Treatment trial, participants predominantly with NYHA Class II or III symptoms and LVEF ≤35% were randomized to enalapril (target dose of 10 mg twice daily) vs. placebo. ACE-inhibitor therapy led to a reduction in mortality and the risk of hospitalization for worsening HF.[9] It is notable that CONSENSUS did not have a specific LVEF inclusion criteria but required the presence of significant left ventricular dilatation. The Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity (CHARM) Alternative trial demonstrated that in patients with an LVEF ≤40% not taking an ACE-inhibitor because of intolerance, the ARB candesartan reduced the primary composite outcome of cardiovascular death or HF hospitalization.[25]

More recently, the Prospective Comparison of ARNI with ACE Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF) enrolled participants with chronic HFrEF. In this trial, sacubitril/valsartan [an angiotensin receptor–neprilysin inhibitor (ARNI)] (target dose of 97/103 mg twice daily) reduced the risk of cardiovascular death or HF hospitalization by 20% when compared with enalapril, the gold-standard ACE inhibitor.[26]

#### Evidence in HFmrEF/HFpEF

The Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) trial compared perindopril with placebo in patients with HF and evidence of diastolic dysfunction on echocardiography without significant systolic dysfunction. No significant difference was reported in the primary composite outcome of all-cause mortality or HF hospitalization after a median follow-up of 2.1 years.[13] There was, however, suggestion of benefit with perindopril at 1 year of follow-up, after which timepoint one fourth of patients discontinued their allocated treatment and began to use open-label ACE-inhibitor at a high rate. The CHARM-Preserved trial compared the ARB candesartan (target dose of 32 mg once daily) with placebo in patients with HF and an LVEF >40% and reported a non-significant reduction of 11% in the primary outcome of cardiovascular death or heart failure hospitalization.[12] In a pre-specified covariate adjusted analysis of the primary outcome, a significant 14% risk reduction was seen with candesartan, which, along with significant reductions in the risk of both time-to-first and the total number of HF hospitalizations, suggested a degree of benefit of candesartan in this population.[12,27] Furthermore, in a subsequent analysis, incorporating all patients enrolled in the CHARM trial programme (i.e. the full spectrum of LVEF), candesartan was shown to significantly

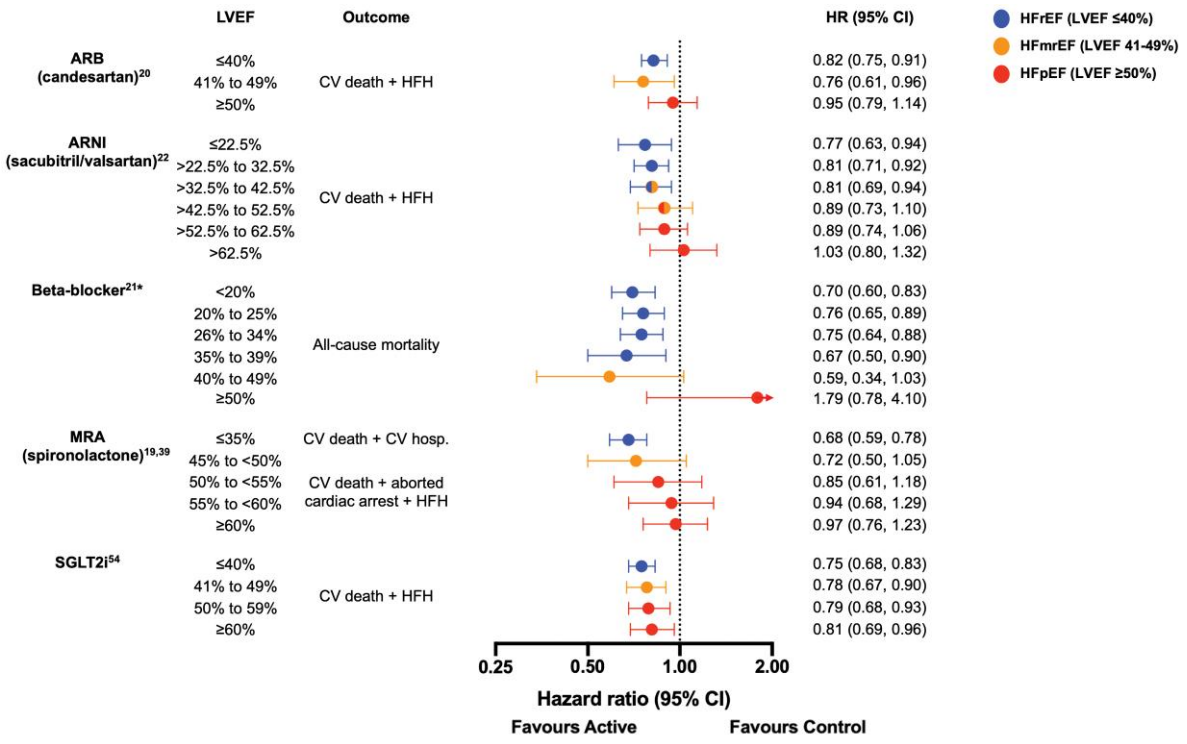


**Figure 1** Effect of HFrEF foundational treatments across the full spectrum of left ventricular ejection fraction. The data presented are derived from *post-hoc* analyses and should therefore be considered as hypothesis generating. *The estimates for beta-blocker subgroups are presented for patients in sinus rhythm only. ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CI, confidence interval; CV, cardiovascular; HFH, heart failure hospitalization; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose co-transporter 2 inhibitor.

reduce the risk of the composite outcome of cardiovascular death and HF hospitalization up to an LVEF of approximately 50% and the risk of recurrent HF hospitalizations up to an LVEF of approximately 60% (*Figure 1*).[20] A further trial with irbesartan in patients aged ≥60 years with an LVEF ≥45% reported no reduction in the primary outcome of all-cause mortality or cardiovascular hospitalization or the secondary endpoint of HF hospitalization.[14] However, in a *post-hoc* covariate adjusted analysis, similar to that pre-specified in CHARM-Preserved, there was the suggestion of potential benefit of irbesartan in patients with HFpEF.[28]

The Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction (PARAGON-HF) trial examined the potential benefit of an ARNI compared with an ARB alone in HF patients with an LVEF ≥45% and elevated natriuretic peptide levels; the rate of the primary composite outcome of total HF hospitalizations and cardiovascular death was lower with sacubitril/valsartan vs. valsartan alone [rate ratio 0.87; 95% confidence interval (CI) 0.75–1.01]; however, this result marginally missed the statistical significance threshold of $P < 0.05$.[16] This result was driven by a non-significant reduction in the number of HF hospitalizations with no between-group difference in the rate of cardiovascular death. A pre-specified subgroup analysis by LVEF ≤ or > than the median (57%) suggested a greater benefit in those with a lower LVEF, with a similar differential effect observed when stratified by sex, with a greater benefit seen in women.[16,29] In an analysis combining the PARADIGM-HF and PARAGON-HF cohorts (i.e. covering the full spectrum of LVEF), a significant treatment-by-LVEF interaction was seen with an attenuation of benefit at LVEF above around 55% (*Figure 1*).[22] When analyzed individually by sex, this relationship was seen to extend to a higher LVEF in women, a finding which has been replicated in *post-hoc* analyses of other neurohumoral modulator trials.[22,23,30]

## Beta-blockers

### Evidence in HFrEF

Data supporting the benefits of beta-blockers in addition to RAS inhibition in patients with HFrEF are provided by five large placebo-controlled trials with a range of LVEF inclusion cut-offs. The United States (US) Carvedilol Heart Failure Study randomized 1094 patients with an LVEF of ≤35% to carvedilol (target dose of 25 mg twice daily) or placebo.[31] The primary outcome of death from any-cause was significantly reduced with carvedilol by 65% (95% CI 39–80%). Furthermore, the risk of hospitalization for cardiovascular reasons was reduced by 27%. Additional evidence supporting the use of carvedilol is provided by the Carvedilol Prospective Randomized Cumulative Survival Study (COPERNICUS) which enrolled 2289 patients with an LVEF <25%; this trial was stopped early due to evidence of benefit of carvedilol in reducing mortality by 35% (95% CI 19–48%) which exceeded the pre-specified interim analyses threshold for benefit.[32] The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II) randomized 2647 patients with an LVEF ≤35% to bisoprolol (target dose of 10 mg

once daily) or placebo and was similarly stopped early due to the finding of a significant 34% reduction in mortality, a benefit predominantly driven by a 44% reduction in the risk of sudden death.[33] Furthermore, the risk of hospitalization for worsening HF was significantly reduced by 36%. The Metoprolol CR/XL Randomised Intervention Trial in-Congestive Heart Failure extended the evidence of beta-blockers to those with an LVEF ≤40% and demonstrated a significant 34% reduction in mortality with metoprolol succinate (target dose of 200 mg daily) vs. placebo, a result which led to the early termination of the trial.[34] The final trial, the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with heart failure (SENIORS), compared nebivolol (target dose of 10 mg once daily) with placebo in 2128 patients with HF and an LVEF of ≤35% but also included patients with a history of HF hospitalization in the preceding year, irrespective of LVEF.[35] Nebivolol reduced the primary composite outcome of time to first cardiovascular hospitalization or death from any-cause by 14% compared with placebo. Death from any-cause was reduced by 12% but this result did not reach statistical significance.

### Evidence in HFmrEF/HFpEF

There have been no large, adequately powered, randomized, placebo-controlled trials of beta-blockers in populations exclusively with an LVEF >40%. As noted above, the SENIORS trial did recruit patients with an LVEF >35% and this group accounted for approximately a third of the trial cohort but only 15% of the overall population had an LVEF >50%. There was no significant modification of the treatment effect on the primary outcome of time to first cardiovascular hospitalization or death from any-cause in a subgroup analysis of those with an LVEF less than or equal to vs. greater than 35%.[35,36] In a meta-analysis of individual patient-level data from 11 placebo-controlled trials with beta-blockers in HF, the Beta-blockers in Heart Failure Collaborative Group reported that the mortality benefits of beta-blockers in HFrEF appeared to extend to those patients with an LVEF of 40–49% (i.e. those with HFmrEF) but not those with an LVEF ≥50% (HFpEF) (*Figure 1*).[21] However, this pattern was observed only in patients with sinus rhythm and not in those with atrial fibrillation, the latter a common comorbidity in patients with HFpEF. These data extended a previous analysis by the same research group which demonstrated that beta-blockers reduced mortality in patients with HFrEF in sinus rhythm but not in those in atrial fibrillation.[37] However, given that the subgroup of patients with HFpEF and chronotropic incompetence had improved functional capacity following beta-blocker withdrawal, more research is needed regarding the role of beta-blockers in patients with heart failure and LVEF > 40%.[38]

## Mineralocorticoid receptor antagonists

### Evidence in HFrEF

Evidence supporting a Class I guideline indication for MRAs to improve outcomes in HFrEF is provided by two large, randomized, placebo-controlled trials. The Randomized Aldactone Evaluation Study (RALES) enrolled 1663 patients with NYHA functional Class III or IV symptoms and an LVEF of ≤35% to spironolactone (target dose of 50 mg once daily) or placebo and reported a significant 30% reduction in both the risk of mortality, the trial's primary endpoint, and the risk of hospitalization for cardiovascular causes.[39] These benefits were also evident in participants with less severe symptoms (i.e. NYHA II) and an LVEF of ≤35% in the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF).[40] Here, the MRA led to a significant 37% reduction in the primary composite outcome of time to first HF hospitalization or cardiovascular death. Moreover, each of the two individual components of the primary outcome were significantly reduced by 42 and 24%, respectively. The results of RALES and EMPHASIS-HF, as well as the demonstrated benefits of eplerenone in patients with left ventricular systolic dysfunction and HF following acute myocardial infarction in the EPHESUS trial, have led MRA to be added to ARNI and beta-blocker as the third pillar of optimal HFrEF therapy.[41]

### Evidence in HFmrEF/HFpEF

In the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial, spironolactone, compared with placebo, did not reduce the primary composite outcome of death from cardiovascular causes, aborted cardiac arrest, or HF hospitalization (hazard ratio 0.89; 95% CI 0.77–1.04) in patients with symptomatic HF and an LVEF ≥45%.[15] There was no difference in cardiovascular death between those randomized to spironolactone or placebo; however, there was a nominally significant 17% reduction in the risk of hospitalization for HF favouring spironolactone. Concerns were raised regarding trial conduct in Russia and Georgia as it was observed that event rates in these regions were similar to the general population. Subsequent analyses by the trial investigators revealed that a sample of patients in these countries randomized to active treatment did not have measurable urinary metabolites of spironolactone. In a subsequent *post-hoc* analysis excluding participants from these regions, a significant 18% reduction in the risk of the primary outcome was reported.[42,43] Further evidence of a potential benefit of spironolactone in patients with HFmrEF/HFpEF was seen in an analysis of TOPCAT which demonstrated greater benefit in patients with an LVEF at the lower end of the range enrolled in the trial (*Figure 1*).[19] Similar findings have been reported for MRAs in a pooled analysis of TOPCAT and the HFrEF trials.[23]

## Sodium-glucose co-transporter 2 inhibitors

### Evidence in HFrEF

SGLT2i are the most recent additions to foundational therapy for HFrEF, with two large, randomized placebo-controlled trials demonstrating benefit in patients with an LVEF ≤40%.

The Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial and the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) reported the benefits of an SGLT2i in reducing the risk of cardiovascular death or worsening HF when added to an RAS inhibitor (including in combination with a neprilysin inhibitor), a beta-blocker, and an MRA.[44–46] In both trials, no modification of treatment effect was observed across the range of LVEF ≤40%.[47,48] Accordingly, current guidelines support

the use of an SGLT2i (dapagliflozin or empagliflozin at a dose of 10 mg once daily) as the fourth foundational therapy for patients with symptomatic HFrEF.[10,11]

### Evidence in HFmrEF/HFpEF

Prior to their role as a treatment for established HF, SGLT2i were investigated as glucose lowering agents in patients with type 2 diabetes and shown to reduce the risk of HF hospitalization irrespective of a history of HF or not.[49] The majority of these analyses did not have granular data with regards to LVEF; however, in those that did, no modification of treatment effect was seen with regards to HF phenotype (HFrEF vs. HFmrEF/HFpEF).[50] Similar benefits were shown with dapagliflozin in patients with chronic kidney disease irrespective of a history of heart failure; no data regarding LVEF were available in this trial though it is reasonable to assume that a proportion of patients with a history of HF had an LVEF >40%.[51]

The results of the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved), the sister trial to EMPEROR-Reduced, was a landmark moment in the management of HF; for the first time in patients with an LVEF of >40%, a treatment was shown to reduce the primary composite outcome of cardiovascular death or HF hospitalization.[17] The pre-specified subgroup analysis by LVEF in the EMPEROR-Preserved trial showed no statistically significant interaction.[17] In a pooled analysis of the EMPEROR programme encompassing the full spectrum of LVEF, the benefits of empagliflozin were consistent in patients with an LVEF <65% with the suggestion of an attenuation of benefit in patients with an LVEF above this *post-hoc* defined threshold.[48] However, the group of patients with an LVEF >65% was a relatively small group (865 out of 9718 patients) with limited number of events ($n = 60$ with HF hospitalization or cardiovascular death in the placebo arm patients with LVEF ≥65%); resulting in large confidence intervals in the effect estimate.[48] Of note, the authors did not find a significant interaction between LVEF analysed as a continuous variable and the effect of empagliflozin in EMPEROR-Pooled.

More recently, the DELIVER (Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure) trial reported the benefit of dapagliflozin in reducing the risk of cardiovascular death or worsening heart failure in patients with an LVEF >40%, including those with a prior LVEF <40% with a degree of improvement in LVEF but ongoing symptoms of HF.[18] In a pooled, individual patient data meta-analysis of the DELIVER and DAPA-HF trials, the benefits of dapagliflozin were seen to be consistent across the full spectrum of LVEF with no evidence of any heterogeneity of treatment effect.[52] Further evidence of benefit in patients with HFpEF who were hospitalized for worsening HF was provided by the Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) trial with no modification of treatment effect whether LVEF was <50% or ≥50%.[53] A meta-analysis including SOLOIST-WHF along with the other four large trials of SGLT2i in HF confirmed a consistent benefit of this drug class across the range of LVEF, reinforcing that SGLT2i can be considered as a treatment for all patients with HF regardless of LVEF.[54]

## International heart failure guidelines

The European Society of Cardiology (ESC) and the American College of Cardiology Foundation/American Heart Association/Heart Failure Society of America (ACCF/AHA/HFSA) have incorporated the four pillars of heart failure therapy into current HF clinical practice guidelines.[10,11] Both guidelines are remarkable for their global reach, influencing clinical practice in countries beyond Europe and the United States. These international guidelines are broadly similar with some specific differences with respect to the role of quadruple therapy in the treatment of HF across the spectrum of LVEF. Of note, both guidelines were published before the DELIVER trial results were known, and the 2021 ESC guidelines were published before the EMPEROR-Preserved trial results were known.

## Similarities between guidelines on the role of quadruple therapy

Both the 2021 ESC and 2022 ACCF/AHA/HFSA guidelines firmly establish that the four pillars of ARNI, evidence-based β-blockers, MRA, and SGLT2i now form the foundational standard of medical therapy for patients with HFrEF (*Figure 2*).[10,11] Each of the four therapies received the highest class of recommendation (Class I). As compared with prior guidelines, SGLT2i were added as a new drug class, and the recommendation for ARNI was upgraded; thus, foundational triple therapy (ACE-inhibitor/ARB, β-blockers, and MRA) was replaced with quadruple therapy for patients with HFrEF.

Both guidelines simplify the foundational treatment approach in HFrEF, no longer dictating the exact sequence of initiation or uptitration of first-line therapies; but instead emphasizing the benefit of establishing all patients on the four pillar medications and optimizing therapeutic doses thereafter. In other words, the guidelines provide the final goal of therapy but allow individualized approaches to get to the goal. Furthermore, both guidelines highlight the urgency to get to goal quickly and recognize an HF hospitalization episode as an opportunity to optimize therapy before discharge and overcome therapeutic inertia. The important role of HF management programmes and post-discharge follow-up are emphasized in both guidelines, as is the multidisciplinary approach including non-pharmacological interventions and holistic management of comorbidities.

Both guidelines also, for the first time, include specific recommendations for HFmrEF.[10,11] This represents a significant advance in the understanding that patients with HFmrEF are likely to benefit from neurohormonal therapies—similar to patients with more reduced LVEF and in contrast to those with higher LVEF (*Figure 1*)—thus providing new treatment options for this group of patients. Yet, some differences exist in the recommendations for HFmrEF and HFpEF between the 2021 ESC and 2022 ACCF/AHA/HFSA guidelines. However, there is one unified recommendation in the guidelines for all patients with HF irrespective of LVEF; the use of diuretics to relieve symptoms of congestion.

## Differences between guidelines on the role of quadruple therapy

There were subtle differences in the recommendations for ARNI use between the 2021 ESC and 2022 ACC/AHA/HFSA

| Drug | Guideline | HFrEF (EF ≤ 40%) | HFmrEF (EF 41-49%) | HFpEF (EF ≥ 50%) |
|---|---|---|---|---|
| ARNI | ESC 2021 | I | IIb | |
| | ACC/AHA/HFSA 2022 | I | IIb | IIb*† |
| BB | ESC 2021 | I | IIb | |
| | ACC/AHA/HFSA 2022 | I | IIb | |
| MRA | ESC 2021 | I | IIb | |
| | ACC/AHA/HFSA 2022 | I | IIb | IIb* |
| SGLT2i | ESC 2021 | I | | |
| | ACC/AHA/HFSA 2022 | I | IIa | |

**Figure 2** Guideline recommendations for quadruple therapy across HF types. ACEi/ARB Class IIb for HFmrEF by both ESC and ACC/AHA/HFSA guidelines; ACC/AHA/HFSA also gives Class III (no benefit) recommendation for nitrates/PDE5i in HFpEF. *Greater benefit in patients with LVEF closer to 50%; †ARB (but not ACEi) given Class IIb recommendation for HFpEF in ACC/AHA/HFSA guidelines. References: McDonagh *et al. Eur Heart J* 2021,[10] Heidenreich *et al. Circulation* 2022.[11] ARNI, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose co-transporter 2 inhibitor; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction.

guidelines. The ESC guidelines were slightly more conservative, giving ARNI an IB recommendation for HFrEF as a replacement for an ACE-inhibitor, while also stating that ARNI may be considered in ACE-inhibitor naive (i.e. *de novo*) patients with HFrEF (Class IIb recommendation).[10] The ACCF/AHA/HFSA guidelines gave ARNI a Class 1A recommendation in NYHA II–III patients with HFrEF in preference to ACE-inhibitors or ARB (with the use of ACE-inhibitors or ARB when the use of ARNI is not feasible).[11]

In HFmrEF, ARNI, ACE-inhibitor, ARB, evidence-based β-blockers, and MRA received Class IIb recommendations in both guidelines; however, the ACCF/AHA/HFSA guidelines also give a Class IIa recommendation for SGLT2i in HFmrEF based on the results of EMPEROR-Preserved which were not available at the time of publication of the ESC guidelines.[10,11]

The ESC guideline recommendations for HFpEF remain largely unchanged compared with prior versions. No class or level of recommendations for medications are given except for diuretics.[10] There is mention of the evidence from retrospective subgroup analyses of trials with ARNI and MRA; however, because these were *post-hoc* analyses with benefit only evident in selected subgroups (i.e. women and participants with LVEF <57% for ARNI; participants recruited in the Americas and LVEF <55% for MRA), the data were not deemed strong enough for a specific recommendations in HFpEF. In contrast, the ACC/AHA/HFSA guidelines gave a Class IIb recommendation for the use of ARNI and MRA in patients with HFpEF, specifically mentioning that benefit with both drug classes is greater in those with LVEF on the lower range, i.e. closer to 50%.[11] Furthermore, the ACC/AHA/HFSA guidelines included a Class IIa recommendation for SGLT2i for the treatment of HFpEF, again based on the results of EMPEROR-Preserved which were not available at the time of publication of the ESC guidelines.[11,17]

Another difference between the guidelines is the inclusion of new value statements in the ACCF/AHA/HFSA guidelines.[11] These are specific recommendations where high-quality cost-effectiveness studies have been published for the intervention under consideration, and their inclusion in the new guidelines represents a significant step forward in guiding therapeutic choices for patients and physicians in resource-limited settings. Notably, all four foundational therapies were considered to provide high economic value in HFrEF. Their high value is despite the fact that neither ARNI nor SGLT2i are generic; yet because of the significant reduction in hospitalizations for treated patients, both therapies provide high economic value in spite of considerable cost.

## Evidence gaps

In considering the role of quadruple therapy across the spectrum of LVEF in HF, it remains debatable if there is an upper LVEF threshold above which there is no benefit, e.g. with SGLT2i, and what precisely that threshold is. LVEF is a continuous variable with a near normal distribution in the general population, making any selected cut-off for the definition of normal vs. abnormal an arbitrary one. The debate is compounded by the fact that there is high variability in LVEF measurements influenced by the type of instrument used (echocardiography vs. magnetic resonance imaging, for instance), the technique (e.g. echocardiographic measurement using biplane Simpson's volumetric measurements vs. Doppler-derived stroke volume vs. visual estimation; the latter fraught with strong digit preference) and the observer (both inter- and intra-observer variation). As noted above with EMPEROR-Preserved and EMPEROR-Pooled, the finding of potential treatment effect modification by LVEF was dependent on the cut-off values used in the analyses and there was no suggestion of an LVEF-by-treatment interaction when ejection fraction was analysed as a continuous variable (or when a similar analysis was conducted in DELIVER with dapagliflozin), highlighting the need to consider all the available data when assessing this question.[48,52] To add to complexity, the

EMPEROR-Pooled analysis of major renal outcomes showed significant heterogeneity in the effect of empagliflozin in HFrEF vs. HFpEF ($P = 0.016$ for interaction), wherein the risk of serious renal outcomes was halved with empagliflozin in EMPEROR-Reduced (HR 0.51; 95% CI 0.33–0.79) but not in EMPEROR-Preserved (HR 0.95; 95% CI 0.73–1.24).[55] However, it is uncertain whether the estimated glomerular filtration rate (eGFR) threshold for decline used in the definition of the renal outcome influenced these findings.[56]

While there has been progress in the understanding of HFmrEF, there remain large evidence gaps regarding the pathophysiology and therapeutic targets in patients with HF and higher LVEF (>60%). Increasing attention has been paid to the detection of cardiac amyloidosis, reported to constitute 6–13% of cases of HFpEF, given the potential to offer these patients effective therapy with the transthyretin tetramer stabilizer tafamadis.[57–59] Similarly, the development of HF in a patient with high LVEF may represent the first presentation of hypertrophic obstructive cardiomyopathy, and this condition may be treated with mavacamten, a cardiac myosin inhibitor.[60] Other potentially treatable causes of HFpEF include pericardial constriction, valvular heart disease, coronary artery disease, high output HF (due to e.g. severe anaemia, arteriovenous shunt, or liver disease), or specific types of myocarditis. The extent to which each of these causes may contribute to HF with high LVEF in unselected practice settings, as well as existence of other potentially treatable causes (e.g. metabolomic or nutritional), represent important knowledge gaps.

Current guidelines define the goal of quadruple therapy in HFrEF but leave open the question of how to initiate and sequence therapies in the individual patient. Numerous strategies have been suggested by experts: One proposal is 'four drugs in four weeks' starting with the simultaneous initiation of a beta-blocker and an SGLT2 inhibitor, followed 1–2 weeks later by the initiation of ARNI, and 1–2 weeks later by an MRA.[61] Another suggestion is the simultaneous initiation of all four pillars of therapy starting with low doses, with rapid uptitration prioritizing beta-blockers.[62] Others have also proposed starting with low dose ARNI and SGLT2i simultaneously, followed within a few days by low dose beta-blocker and MRA, followed by uptitration.[63] None of the proposed sequencing methods have been tested in prospective trials. Given the benefits of SGLT2i across the full spectrum of ejection fraction and the evidence of early benefit with this therapy, it has been suggested that treatment with SGLT2i may be considered in newly diagnosed patients with HF prior to echocardiography to delineate their LVEF phenotype.[52,54]

Guidance is also needed regarding the sequencing of second line therapies following the foundational four first-line medications. Data-centric approaches to quantify the relative benefit and estimate the life years gained from various combinations of therapies have been published.[64] The Heart Failure Association of the ESC has suggested a patient profiling approach, tailoring therapeutic selection to patient characteristics such as heart rate and rhythm, blood pressure, renal function, and potassium level.[65] An HF spending function 'investment' framework has also been proposed, whereby each patient is conceptualized to have reserve 'banks' in physiological and psychosocial domains (i.e. blood pressure, heart rate, serum creatinine, potassium, and out-of-pocket costs), and those are spent by medication initiation/intensification for a future return on investment in terms of clinical benefit.[66] The goal would therefore be to optimize spending from all domain reserves for the greatest return of investment, recognizing that with underspending, patients fail to gain the full benefit of all available therapies; conversely with over-spending, addition of new drugs or higher doses that draw upon a domain may lead to patient harm. While intuitive, further healthcare delivery research is needed to validate and refine the clinical implementation of these strategies. As more therapies become available, the time may come to perform withdrawal trials to test if older 'legacy' medications still have a place in the current era of quadruple therapy.[67]

One of the most notable advances with quadruple therapy is the ability not only to improve cardiovascular outcomes, but also renal outcomes with SGLT2i in particular. However, the safety and efficacy of SGLTi has been established in patients with chronic kidney disease (CKD) stages 1 to 4, and currently, data are lacking in CKD stage 5 and patients on renal replacement therapy.[68]

## Future directions

Inspection of *Figure 1* suggests broadly similar patterns of response across the spectrum of LVEF values which are below the normal range (i.e. patients with HFrEF and HFmrEF) in each of the four pillars of HFrEF therapy. Only SGLT2i can be considered as having evidence of benefit in all patients with HF regardless of LVEF.[52,54]

While the threshold of LVEF at which the point estimates of hazards ratios cross unity vary, they appear largely below 1 (indicating benefit from therapy) up to an LVEF of 55 or 60%. These LVEF values coincide with those used to define 'normal' in the general population, as recommended in echocardiography guidelines.[69] Thus, patients with HF and LVEF above these 'normal' thresholds may be more appropriately named 'HF with normal LVEF'.[70,71]

Given evidence suggesting benefit with quadruple therapy in patients not only with HFrEF but up to an LVEF below normal (*Figure 1*), we foresee a future where the approach to HF may be simplified to classifying patients as having an LVEF less than normal (i.e. reduced) and those with normal LVEF. The former would be strongly considered for quadruple therapy as detailed in the preceding sections. The lack of current consensus in guidelines as to treatment for patients with HFpEF highlights the differences which exist in interpretations of the existing data and that new data in this area are being published faster than guidelines can be updated.[10,11] Further evidence that the reliance on rigid LVEF cut-offs may also be outdated is provided by the United States Food and Drug Administration's (FDA) approval of ARNI for HF which does not state that benefits are restricted to those with HFrEF or HFpEF—but rather that 'benefits are most clearly evident in patients with LVEF below normal' and 'LVEF is a variable measure, so use clinical judgment in deciding whom to treat'.[72] This guidance is not, however, without contention, as evidenced by the ESC guideline's decision not to offer a recommendation for sacubitril/valsartan in patients with an LVEF ≥50% and that the FDA approval may not be universally replicated elsewhere in the world.[10]

As is the case with HFrEF and HFmrEF, for patients with HF and normal LVEF, components of quadruple therapy may still find clinical application in the management of the aetiology or comorbidities of HF (e.g. beta-blockers for coronary artery disease or atrial fibrillation, SGLT2i for diabetes, or CKD). Adequate management of congestion (with diuretics) and a careful search for potential treatable causes (e.g. amyloidosis, hypertrophic obstructive cardiomyopathy) and precipitants (e.g. arrhythmia, ischaemia) should also be performed in these patients. Furthermore, the non-pharmacological management of HF, including fluid and salt restriction, exercise training, and cardiac rehabilitation, is the same across the LVEF spectrum.

Importantly, the definition of 'normal' LVEF varies with demographic and clinical factors such as age, sex, and ethnicity.[30,73] Clinical judgement is, therefore, essential in the determination of who may have HF with reduced LVEF and be suitable for quadruple therapy. For instance, the normal LVEF is, on average, higher in women than men at a given age. Thus, in a patient with HF, an LVEF of 55% may be reduced for a woman but not for a man, warranting consideration of quadruple therapy for the woman. Indeed, retrospective analyses across the spectrum of LVEF in HF have shown that women appear to benefit from guideline-directed medical therapies to a higher LVEF compared to men.[23]

Furthermore, it is critical to recognize that the term 'normal' in referring to 'HF with normal EF' does not mean that these are healthy individuals with a good prognosis. On the contrary, recent large echocardiographic studies inclusive of patients with HF have shown that patients with a higher LVEF have a worse prognosis than those at the risk nadir of LVEF~60% and a greater risk of mortality at higher LVEF among women.[74,75]

## Conclusions

Quadruple therapy with ARNI, beta-blockers, MRA, and SGLT2i has been established as first-line therapy for patients with HFrEF in current heart failure guidelines. There is increasing evidence that many patients with HF with an LVEF >40% may benefit from these medications. SGLT2i have been shown to be beneficial in HF regardless of ejection fraction. This review of the evidence for these treatments across the entire spectrum of LVEF suggests the possibility that the approach to HF therapy, while still guided by LVEF, can be simplified. Specifically, patients could be classified into one of two groups: those with reduced LVEF and those with normal LVEF, where 'normal' is clearly higher than 50% and depends on demographic and clinical factors. Evidence gaps in those with higher LVEF in the normal range need to be addressed.

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