

Clinical Profile-Based Pharmacological Sequencing for Heart Failure with Preserved Ejection Fraction

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Introduction

Heart failure (HF) is classically categorized into phenotypes according to left ventricular ejection fraction (EF), one of them being HF with preserved EF (HFpEF; EF \geq 50%).¹ In the past decades, a myriad of drug therapies that reduce mortality and hospitalization rates for HF with reduced EF have emerged. However, although HFpEF accounts for about 50% of HF cases, to this date, only empagliflozin was shown to reduce HF hospitalization, and no drug reduced the risk for cardiovascular death in randomized clinical trials (RCTs).² One hypothesis that may explain the lack of therapies that reduce hard outcomes in HFpEF is the variety of phenotypes that constitute HFpEF as a syndrome.³ Thus, in this paper, we discuss evidence from RCTs and post-hoc analyses of RCTs that may help improve HFpEF outcomes, aid clinicians, and pave the way for future RCTs.

Clinical phenotypes of heart failure with preserved ejection fraction

HFpEF is a clinical syndrome arising from the interaction of multiple comorbidities that leads to an inflammatory state that produces cardiac and extracardiac abnormalities.³ Because of the diversity of comorbidities that can lead to HFpEF, this clinical syndrome is highly heterogeneous, which may explain why RCTs investigating a one-size-fits-all treatment have failed to reduce cardiovascular mortality among patients with HFpEF.³ Previous studies using machine-learning techniques have identified different phenogroups consisting of a combination of clinical features (pulmonary hypertension, lung congestion, atrial fibrillation, skeletal muscle weakness, and chronotropic incompetence),^{4,5} as illustrated in Figure 1. In addition to different clinical characteristics, these phenogroups have prognostic particularities and appear

to respond differently to medical therapies.^{4,5} Therefore, classifying patients with HFpEF into phenogroups according to their clinical features could constitute a key aspect to guide medical therapy.

Evidence-based drug therapies for heart failure with preserved ejection fraction

As mentioned before, although there is a variety of drugs that improve outcomes for HF with reduced EF, this is not the case with HFpEF. One key step of HFpEF management is to treat etiologies and comorbidities (eg, hypertension, diabetes, coronary artery disease, obesity, anemia, chronic kidney disease, etc).¹ This may reduce not only disease progression but also HF hospitalization.¹ Regarding disease-modifying therapies, only empagliflozin is supported by robust evidence from an RCT to justify its use for HFpEF.² However, post-hoc analyses of RCTs indicate that other drug therapies may also reduce outcomes in HFpEF. This is mainly illustrated by the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial, in which spironolactone did not reduce the primary outcome in patients with HFpEF compared with placebo, although it was effective among patients with elevated natriuretic peptides.^{6,7} Also, surprisingly, patients in the Americas experienced an 18% risk reduction in the primary outcome, whereas in Russia and Georgia, spironolactone did not improve prognosis.⁶ A post-hoc analysis of the CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients (CHAMPION) trial also showed that changes in diuretic and vasodilator therapies according to pulmonary artery pressure reduced by 46% the incidence ratio of HF hospitalization in HFpEF with New York Heart Association (NYHA) class III.⁸ Therefore, this may indicate that diuretics may not only control HF symptoms but also reduce HF hospitalization. Finally, although the Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction (PARAGON-HF) trial showed no benefit of sacubitril-valsartan for HFpEF, a prespecified analysis of this RCT showed that sacubitril-valsartan reduced the primary outcome in women with HFpEF due to a reduction in HF hospitalization.⁹ In Table 1, we detail phase III RCTs that have investigated pharmacological therapies for HFpEF.

Keywords

Heart Failure; Mineralocorticoid Receptor Antagonists; Angiotensin-Converting Enzyme Inhibitors; Adrenergic Beta-Antagonists; Digoxin.

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Manuscript received February 25, 2022, revised manuscript February 25, 2022, accepted March 07, 2022

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As reviewed above, in addition to etiologic treatment, there are 3 drug therapies that may benefit patients with HFpEF based on RCTs (empagliflozin), post-hoc analyses of RCTs (mineralocorticoid receptor antagonists), and indirect

DOI: <https://doi.org/10.36660/abchf.20220014>

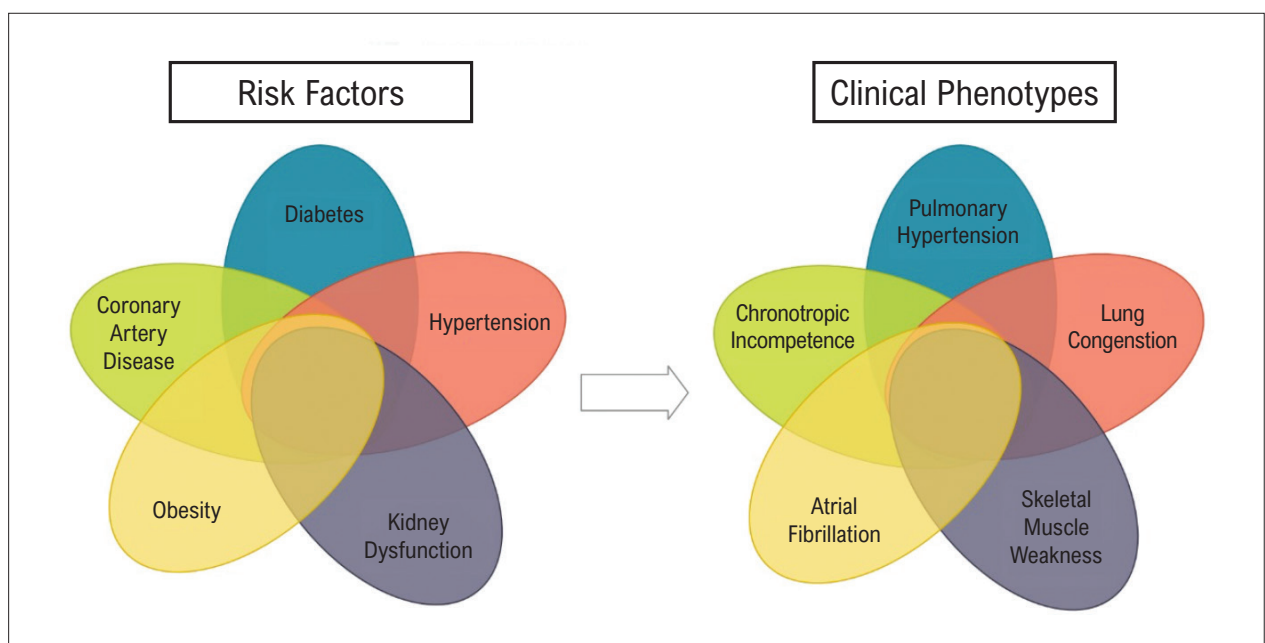


Figure 1 – Interaction of cardiometabolic risk factors that produce a complex combination of clinical features with consequent unique phenotypes of heart failure with preserved ejection fraction.

Table 1 – Phase III randomized controlled trials of pharmacological therapies for heart failure with preserved ejection fraction

Study	Drug	LVEF Range	Other Inclusion Criteria	All-Cause Mortality	CV Mortality	CV Death or HF Hospitalization	HF Hospitalization
PEP-CHF	Perindopril	LV wall motion index ≥ 1.4	Symptomatic HF treated with diuretics, diastolic dysfunction, age ≥ 70 years	1.09 (0.75-1.58)	0.98 (0.63-1.53)	NR	0.86 (0.61-1.20)
CHARM-Preserved	Candesartan	$> 40\%$	NYHA class II-IV, history of CV hospitalization	NR	0.99 (0.80-1.22)	0.89 (0.77-1.03)	0.85 (0.72-1.01)
I-PRESERVE	Irbesartan	$\geq 45\%$	NYHA class III-IV or NYHA class II with HF hospitalization in the past 6 months, age ≥ 60 years	1.00 (0.88-1.14)	1.01 (0.86-1.18)	0.96 (0.84-1.09)	0.95 (0.81-1.10)
PARAGON-HF	Sacubitril-valsartan	$\geq 45\%$	NYHA class II-IV, left atrial enlargement or LV hypertrophy and elevated BNP ≥ 300 pg/mL or NT-proBNP ≥ 900 pg/mL or HF hospitalization in the past 9 months	0.97 (0.84-1.13)	0.95 (0.79-1.16)	0.87 (0.75-1.01)	0.85 (0.72-1.00)
TOPCAT	Spironolactone	$\geq 45\%$	≥ 1 HF sign and ≥ 1 HF symptom, HF hospitalization within the past 12 months, or BNP ≥ 100 pg/mL or NT-proBNP ≥ 360 pg/mL, age ≥ 50 years	0.91 (0.77-1.08)	0.90 (0.73-1.12)	0.89 (0.77-1.04)	0.83 (0.69-0.99)
EMPEROR-Preserved	Empagliflozin	$\geq 40\%$	NYHA class II-IV, 18 years or older, NT-proBNP > 300 pg/mL or NT-proBNP > 900 pg/mL for patients with HF and AF	1.00 (0.87-1.15)	0.91 (0.76-1.09)	0.79 (0.69-0.90)	0.73 (0.61-0.88)
DIG-PEF	Digoxin	$> 45\%$	SR	0.99 (0.76-1.28)	1.00 (0.73-1.36)	0.88 (0.70-1.11)	0.79 (0.59-1.04)

AF: atrial fibrillation; CV: cardiovascular; HF: heart failure; LV: left ventricular; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal prohormone B-type natriuretic peptide; NYHA: New York Heart Association; S: sinus rhythm

Viewpoint

evidence from RCTs (diuretics).^{2,7,8} Also, personalizing HFpEF treatment according to clinical presentation and presence of risk factors, similar to what is done in other syndromes, could benefit patients with HFpEF and seems to be a better option than focusing on a one-size-fits-all treatment.³ In Table 2, we suggest a pharmacological approach to treat patients with HFpEF according to their clinical presentation and risk factors, similar to that described by Shah et al.³ but in light of new evidence from RCTs and post-hoc analyses reviewed in this paper.

Perspectives

The heterogeneity of HFpEF as a syndrome may explain why all RCTs have failed to observe a significant reduction in cardiovascular mortality in this population. New RCTs selecting a specific population of patients with HFpEF with a unique set of clinical features and risk factors might reveal effective medical therapies to be adopted by HF guidelines. For instance, Park et al. demonstrated that, for patients with HF with EF > 40% and a global longitudinal strain < 14%, the use of beta-blocker therapy was associated with improved survival, while for those with a global longitudinal strain > 14%, the same was not true.¹⁰ However, the characterization of HFpEF phenotypes is under development, and there is still room for future large-scale multicenter studies using novel biomarkers and imaging techniques to better recognize HFpEF phenotypes.

Conclusions

Although HFpEF accounts for about 50% of HF cases, there is a lack of therapies that reduce cardiovascular death.

Shifting from a one-size-fits-all approach to a clinical profile-based pharmacological strategy may be the key to produce a significant reduction in hard outcomes in HFpEF. However, although conceptually sound, this therapeutic model still needs to be validated by RCTs.

Author Contributions

Conception and design of the research, Analysis and interpretation of the data and Writing of the manuscript: Mesquita ET, Correia ETO, Barbeta LMS; Acquisition of data: Correia ETO; Critical revision of the manuscript for intellectual content: Correia ETO, Barbeta LMS.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Table 2 – Pharmacological strategy for heart failure with preserved ejection fraction according to clinical profile and risk factors. Clinical phenotypes and table adapted from Shah et al.³

	Lung Congestion	Chronotropic Incompetence	Pulmonary Hypertension	Skeletal Muscle Weakness	Atrial Fibrillation
Obesity	Diuretics/MRA/SGLT2i/ARNI (for women)/caloric restriction	MRA/SGLT2i/ARNI (for women)/caloric restriction/atrial pacing	MRA/SGLT2i/ARNI (for women)/caloric restriction/PDE	MRA/SGLT2i/ARNI (for women)/caloric restriction/exercise training	MRA/SGLT2i/ARNI (for women)/caloric restriction/cardioversion or rate control/anticoagulation
Diabetes	Diuretics/MRA/SGLT2i/ARNI (for women)/caloric restriction	MRA/SGLT2i/ARNI (for women)/caloric restriction/atrial pacing	MRA/SGLT2i/ARNI (for women)/caloric restriction/PDE	MRA/SGLT2i/ARNI (for women)/caloric restriction/exercise training	MRA/SGLT2i/ARNI (for women)/caloric restriction/cardioversion or rate control/anticoagulation
Hypertension	Diuretics/MRA/SGLT2i/ARNI (for women), ACEi or ARB	MRA/SGLT2i/ARNI (for women), ACEi or ARB/atrial pacing	MRA/SGLT2i/ARNI (for women), ACEi or ARB/PDE	MRA/SGLT2i/ARNI (for women), ACEi or ARB/exercise training	MRA/SGLT2i/ARNI (for women), ACEi or ARB/cardioversion or rate control/anticoagulation
Kidney Dysfunction	Diuretics/MRA/SGLT2i/ARNI (for women)/ultrafiltration if needed	MRA/SGLT2i/ARNI (for women)/ultrafiltration if needed/atrial pacing if needed	MRA/SGLT2i/ARNI (for women)/ultrafiltration if needed/PDE	MRA/SGLT2i/ARNI (for women)/ultrafiltration if needed/exercise training	MRA/SGLT2i/ARNI (for women)/ultrafiltration if needed/cardioversion or rate control/anticoagulation
CAD	Diuretics/MRA/SGLT2i/ARNI (for women), ACEi or ARB/revascularization	MRA/SGLT2i/ARNI (for women), ACEi or ARB/revascularization/atrial pacing if needed	MRA/SGLT2i/ARNI (for women), ACEi or ARB/revascularization/PDE	MRA/SGLT2i/ARNI (for women), ACEi or ARB/revascularization/exercise training	MRA/SGLT2i/ARNI (for women), ACEi or ARB/revascularization/cardioversion or rate control/anticoagulation

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; ARNI: angiotensin receptor-neprilysin inhibitor; CAD: coronary artery disease; MRA: mineralocorticoid receptor antagonist; PDE: phosphodiesterase inhibitor; SGLT2i: sodium-glucose cotransporter 2 inhibitor.

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