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Management Strategies for Heart Failure with Preserved Ejection Fraction (HFpEF): A Systematic Review and Meta-analysis

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Systematic Review Article

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ABSTRACT

Background: Heart failure with preserved ejection. Fraction is a set of clinical symptoms that raises mortality and morbidity. It should be addressed promptly and appropriately.

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Aims: The current systematic review examines management strategies for heart failure patients with preserved ejection fraction (HFpEF).
Materials and Methods: PICOS scheme was followed in the development of eligibility criteria. Different databases like PubMed, Google Scholar, etc were searched for the primary studies.
Results: The final sample included 21 studies that were manually selected. This meta-analysis found that beta-blockers and ace inhibitors significantly reduced mortality and hospitalizations as primary outcomes.
Conclusion: To summarize, the study found that beta blockers and ACE inhibitors reduce mortality in heart failure patients with preserved ejection fraction. However, more research is needed to support this study.

Keywords: Management strategies; heart failure; preserved ejection fraction; inhibitors.

ABBREVIATIONS

HF	*: Heart Failure*
SOB	*: Shortness of Breath*
HFpEF	*: Heart Failure Patients with Preserved Ejection Fraction*
ACE inhibitors	*: Angiotensin Converting Enzyme Inhibitors*
MRAs	*: mineralocorticoid receptor antagonists*
RCTs	*: randomized controlled trials*
CV Mortality	*: Cardiovascular Mortality*
LV Function	*: Left Ventricular Function*
TOPCAT	*: Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist*

1. INTRODUCTION

Heart Failure (HF) is a clinical condition, that can be termed a syndrome because it consists of multiple symptoms like shortness of breath (SOB), fatigue, generalized body edema, and inability to do physical activities normally [1]. This is due to the inability of the heart to meet bodily needs. About 6 million people in the US have been officially diagnosed with heart failure, which translates to an estimated 2.5% of the country's population having the illness [2]. It was discovered that roughly 1.6% of people in the UK receive care in general practice, according to a study involving 4 million patients [3]. It's crucial to remember that there is a subset of patients who do not have a diagnosis of heart failure, indicating that the true prevalence of the illness is most likely higher than previously stated [4]. When compared to patients diagnosed with HFrEF and HFmrEF, individuals affected by HFpEF are typically older and more often female [5,6]. Moreover, diabetes, obesity, hypertension, chronic kidney disease, and decreased physical fitness, are frequently present in people with HFpEF [7]. Furthermore, a few medical disorders may cause HFpEF. Primary cardiomyopathies, pericardial diseases like constrictive pericarditis, and storage disorders like Fabry's disease and amyloidosis are among them [8].

Although data from clinical trials frequently imply that HFpEF may have superior survival outcomes than HFrEF [9], the majority of observational studies show that there is little to no difference in survival between the two types of heart failure [4].

In light of this data, HFpEF is recognized as a growing epidemiological concern because of its high death rates, the spiraling expenses linked to repeated hospital stays, the detrimental effects on years lost from work, and patient-reported outcomes that impair quality of life [10]. The urgent need for early management of heart failure with preserved ejection fraction (HFpEF) is highlighted by this systematic review and meta-analysis (SRMA) because of the substantial effects of HFpEF on patient quality of life, healthcare costs, and mortality.

1.1 Objectives

The main objective of this systematic review and meta-analysis is to compare the efficiency of various pharmaceutical treatments in lowering HFpEF patients' all-cause mortality. The management strategies that work the best for HFpEF while lowering all-cause mortality, cardiovascular mortality as well as hospitalization rates. This will help future clinicians and researchers to devise strategies that are at the best interest of patients with HFpEF.

2. METHODOLOGY AND MATERIALS

2.1 Eligibility Criteria

The PICOS scheme was followed in the development of eligibility criteria [11]. The

inclusion criteria were: (i) Research involving adult patients who meet established diagnostic criteria and are diagnosed with heart failure with preserved ejection fraction (HFpEF). (ii) Research on the use of pharmacological interventions, such as angiotensin receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACEIs), beta-blockers, mineralocorticoid receptor antagonists (MRAs), diuretics, and innovative therapies, for the management of HFpEF. (iii) Research evaluating the effects of various pharmacological treatments for HFpEF on hospitalization rates, cardiovascular mortality, and all-cause mortality. (iv) Research presenting numerical information on hospitalization rates, cardiovascular mortality, and all-cause mortality linked to pharmaceutical intervention use in HFpEF patients. (v) observational cohort studies, and randomized controlled trials (RCTs). (vi) English-language studies published. (vii) There are no deadlines for publication.

The following are the *exclusion* criteria: (i) Research using animal models or pediatric populations. (ii) Conference abstracts, editorials, commentaries, letters, review articles, and meta-analyses. (iii) Research lacking pertinent outcome information on hospitalization rates, cardiovascular mortality, or all-cause mortality linked to pharmaceutical interventions in patients with HFpEF. (iv) Studies that are not written in English because there might not be enough resources for translation. (v) Research with poor methodological quality, such as those with a high bias risk or insufficient disclosure of important study parameters. (vi) Research involving non-pharmacological interventions for HFpEF management. (Table 1)

2.2 Information Sources

Different databases like PubMed, Google Scholar, etc were searched for the primary studies.

2.3 Search Strategy

("heart failure, preserved ejection fraction"[MeSH Terms] OR "heart failure, preserved ejection fraction"[Title/Abstract] OR "HFpEF" [Title/Abstract]) AND ("pharmacological therapy" [MeSH Terms] OR "pharmacological therapy "[Title/Abstract] OR "pharmacological intervention "[MeSH Terms] OR "pharmacological intervention "[Title/Abstract]) AND ("mortality"[MeSH Terms] OR "mortality" [Title/Abstract] OR "hospitalization"[MeSH Terms] OR "hospitalization"[Title/Abstract]).

2.4 Selection Process

The search approach was created using publications and peer-reviewed journals. Using the PICOS scheme, the literature that met the inclusion criteria was carefully examined. Rayyan.ai, a screening program, received all of the chosen articles for screening as primary and secondary literature [12]. Researchers worked together to use the inclusion and exclusion criteria to "include" or "exclude" relevant papers.

Table 1. Eligibility Criteria

Criteria	Inclusion	Exclusion
Population	Adult patients diagnosed with HFpEF	Pediatric populations, animal studies
Intervention	Pharmacological interventions for HFpEF management	Non-pharmacological interventions, interventions unrelated to HFpEF management
Comparison	Studies comparing different pharmacological interventions for HFpEF	Studies without comparative data on pharmacological interventions
Outcomes	All-cause mortality, cardiovascular mortality, hospitalization rates associated with pharmacological interventions in HFpEF patients	Studies lacking relevant outcome data or sufficient methodological quality
Design of Studies	RCTs, observational cohort studies	Review articles, meta-analyses, editorials, letters, conference abstracts
Language	English language	Non-English language
Publication Date	No restrictions	Studies with insufficient methodological quality, duplicate publications, inadequate sample size

Table 2. Table showing the column headings within the Data Extraction Table

Sr No.	Study	Country	Study Design	Population	Sample Size	Intervention	Outcome measured

2.5 Effect Measures

The studies included in the meta-analysis underwent a thorough analysis and data was extracted for All-cause mortality, Cardiovascular Mortality, Hospitalization, Incidence of Myocardial Infarction, and Stroke. Events and Totals were extracted and tabulated in an Excel Sheet. The studies were listed in Cochrane RevMan 5.4 software and meta-analysis was performed.

2.6 Assessment of Research Quality

-*systematic review:* All primary studies that were chosen for quality assessment had their study bias evaluated. Manual reviews were conducted of the population demographics, the intervention features of the studies, and their outcome domains. Every study that was chosen for meta-analysis was subjected to the Cochrane Risk of Bias (ROBvis2) tool for quality assessment.

- *meta-analysis:* We searched for online and digital resources to assess the degree of "bias" in the selected studies. Every primary study, or RCT that met the criteria for analysis, was selected independently using the "Cochrane" criteria to evaluate bias. The areas where bias could exist were [13]. (1) the generation of a random sequence; (2) the hiding of allocations; (3) participant and staff blinding; (4) the blinding of outcome assessments; (5) the attrition bias, or lack of sufficient outcome data; (6) the reporting bias, or selective reporting; and (7) additional biases. For every RCT, the quality assessment was presented as a "traffic lights" plot. In addition, we generated a "forest plot" for the meta-analysis using Review Manager (RevMan version 5.4). A meta-analysis of primary studies was performed using Rev-man (version 3.5.1) software. Three researchers collected poolable and comparable data for the analytical tool [14]. All of the data was available as continuous variables.

2.7 Synthesis Methods

The Table 3 was used as a standard template to extract data from the primary studies. For secondary screening, the Rayyan ai tool was used. Title, name of author, year, nation, population, design of study, sample size, intervention, comparison, and, Results were taken out. (Table 2)

3. RESULTS

Data: The total sample size (n=21) for the selected literature was assessed after the secondary screening procedure was finished. We used the Preferred Reporting Items for Systematic Review and Meta-Analysis standards [15] to create a PRISMA flow diagram for the selected studies from journals and other independent resources (if the reports were available). (Fig. 1). The following steps were taken to lessen analysis bias: (1) selecting high-quality research; (3) requiring conflict of interest disclosure from peer reviewers. In order to uphold the standards of the study, narrative reviews, and systematic reviews were disregarded. Using randomization, a "traffic light" figure was produced based on this data. (Fig. 1)

Study Characteristics: A total of 21 studies are included in this systematic review and meta-analysis. All of the studies are Randomized Controlled Trials evaluating the effects of different drugs on Heart Failure with Preserved Ejection Fraction. The study Characteristics of all of the studies are given below. (Table 3)

Quality Assessment: The “traffic Light Plot” is generated and given below. (Fig. 2)

Meta-Analysis: A comprehensive meta-analysis was done with these outcomes: (i) All-cause Mortality, (ii) CardioVascular Mortality, (iii) Stroke, (iv) Myocardial Infarction, and (v) Hospitalization. All the data extracted from the primary studies was dichotomous and RevMan 5.4 software was used. The forest Plots for each variable were made.

All-Cause Mortality: It is a dichotomous variable and Events and Totals were extracted for the experimental as well as control groups of each primary study. Random effects model is used to

calculate Risk Ratio. Different drugs from Irbesartan [17], B blockers [19], B blockers [20], Serelaxin [21], ARNI [24], Spironolactone [26], Carvedilol [27], Perindopril [29], Digoxin [31], Nebivolol [32], ANRI [34], and Spironolactone [36]. The overall RR was found to be 0.98 [0.94, 1.02]. Perindopril (Ace inhibitors) and beta blockers were shown to have positive effects on all-cause mortality in Heart Failure with Preserved Ejection Fraction. (Fig. 3)

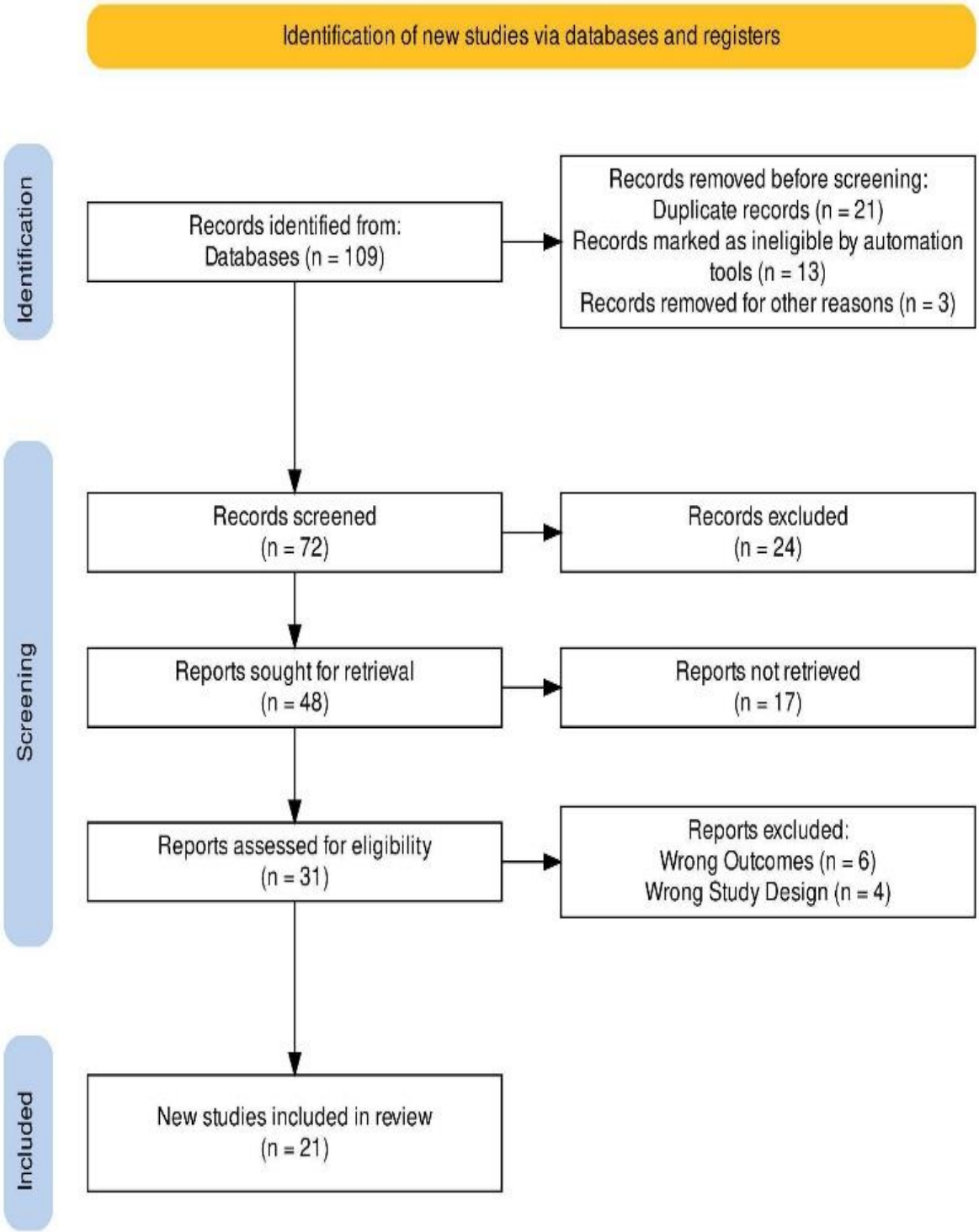

Fig. 1. PRISMA Flow Chart of the included studies

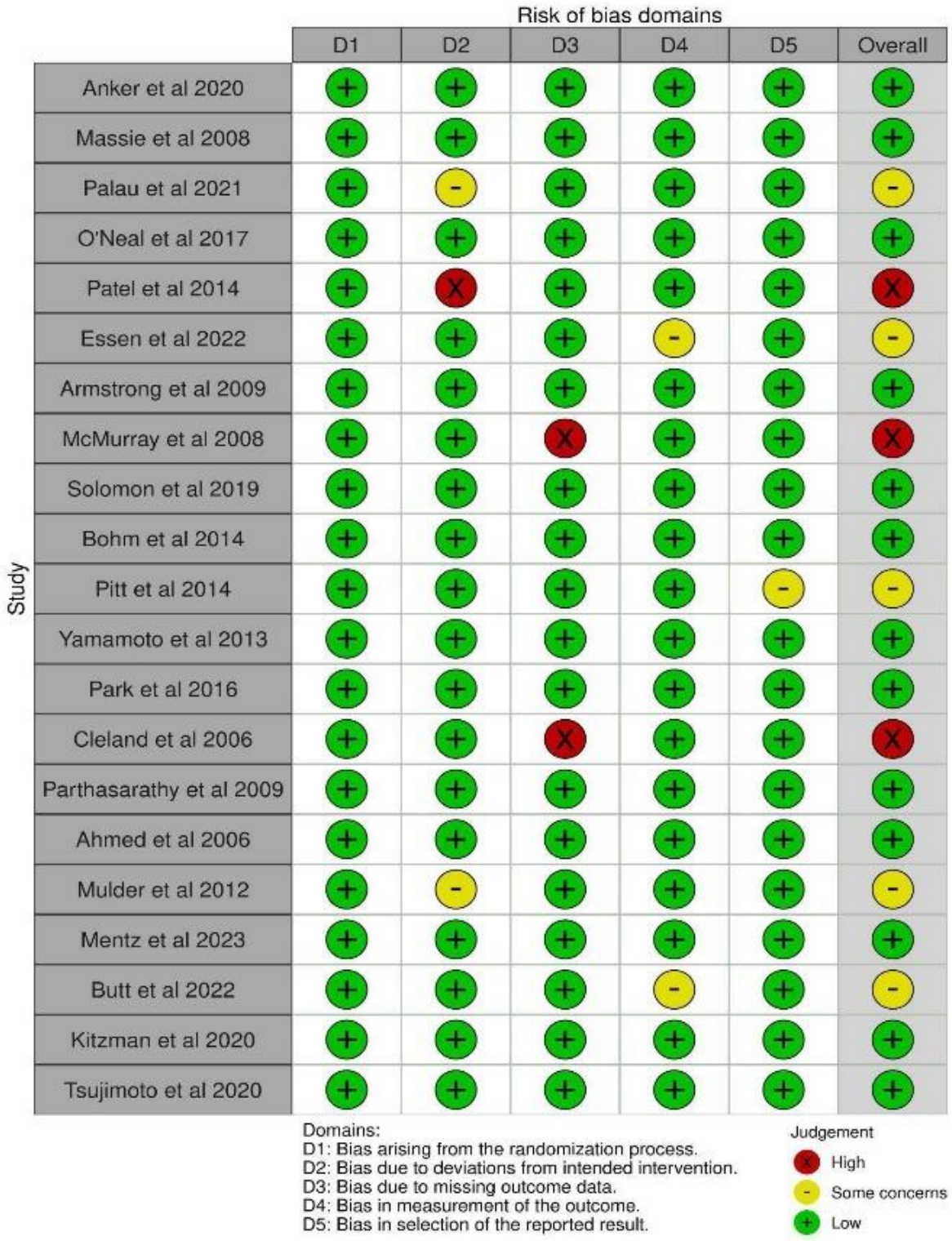

Fig. 2. Traffic Light Plot of the included studies

Table 3. Summary Table of the Included Studies [16-36]

Sr No	Study	Location	Study Design	Population	Sample Size	Intervention	Comparison	Outcomes	Results
1	Anker et al 2020 [16]	Germany, USA, Korea	RCT-EMPEROR-Preserved trial	Adults aged more than 18 years with chronic heart failure	11,585	SGLT2 cotransporter inhibitor (Empagliflozin)	Placebo	mortality and morbidity	This is a baseline characteristics' study for the EMPEROR trial.
2	Massie et al 2008 [17]	USA	Randomised Controlled Trial	Patients with HFpEF	4128	Irbesartan (300mg daily)	Placebo	Death, hospitalization, Stroke, MI, Arrythmias	Patients did not respond better to irbesartan.
3	Palau et al 2021 [18]	Spain	Randomised Controlled Trial	Patients with HFpEF	52	Beta Blockers	Placebo	peak VO2 and percentage of predicted peak VO2	Patients with HFpEF showed improved maximal functional capacity after stopping their b-blockers. B-blocker use in HFpEF requires a thorough reassessment.
4	O'Neal et al 2017 [19]	USA	Clinical Trial (analysis from TOPCAT trial)	Patients with HFpEF	2705	Beta blockers, ACE inhibitors, Spironolactone	Placebo	Mortality, Hospitalization, Morbidity	Future research is required to ascertain whether lowering heart rate in patients with HFpEF improves outcomes, as high resting heart rate is a risk factor for unfavorable outcomes in this population.

Sr No	Study	Location	Study Design	Population	Sample Size	Intervention	Comparison	Outcomes	Results
5	Patel et al 2014 [20]	USA	Clinical Trial	Older Patients with HFpEF	2198	Beta Blockers	Placebo	all-cause mortality or HF rehospitalization	New beta-blocker discharge prescriptions had no correlation with the primary composite endpoint of all-cause mortality or HF rehospitalization over the course of a 6-year follow-up.
6	Essen et al 2022 [21]	Netherlands	Randomised Controlled Trial	acute heart failure with a supranormal left ventricular ejection fraction	6128	Serelaxin	Placebo	All-cause mortality, HF rehospitalization, cardiovascular mortality	The main characteristics of HFsnEF were higher risk of non-CV death, lower levels of natriuretic peptides, and female sex.
7	Armstrong et al 2009 [22]	Canada	Clinical Trial	Older Patients with Heart Failure	2000	Nebivolol (Beta Blocker)	Placebo	mortality and cardiovascular hospital readmission	Beta blockers improved outcomes in patients with HFpEF.
8	McMurray et al 2008 [23]	UK, USA	Randomised Controlled Trial	HFpEF	4133	Irbesartan	Placebo	Baseline Chracteristics of I-PRESERVE Trial	Because the patients in I-PRESERVE are largely representative of those observed in epidemiological studies, the trial's findings should be broadly applicable

Sr No	Study	Location	Study Design	Population	Sample Size	Intervention	Comparison	Outcomes	Results
									to patients with heart failure and preserved ejection fraction in the "real world."
9	Solomon et al 2019 [24]	USA	Randomised Controlled Trial	HFpEF	4822	sacubitril–valsartan (target dose, 97 mg of sacubitril with 103 mg of valsartan twice daily) or valsartan (target dose, 160 mg twice daily)	sacubitril–valsartan or valsartan	All-cause mortality, HF rehospitalization, cardiovascular mortality	The combination of sacubitril and valsartan did not significantly reduce the overall hospitalization rate for heart failure or the rate of cardiovascular death in patients with heart failure.
10	Bohm et al 2014 [25]	Multiple Countries	Randomised Controlled Trial	HFpEF	3967	a beta-blocker, calcium channel blocker, or digoxin	Placebo	All cause death or CV hospitalization, CV death or HF hospitalization, All-cause death, CV death, HF hospitalization	The two main side effects of HF-PEF, which are cardiovascular death and Hospitalization due to heart failure suggests a possible therapeutic approach in a condition for which there isn't a proven cure.
11	Pitt et al 2014 [26]	USA	Randomised Controlled	HFpEF	3445	Spironolactone	Placebo	All cause death or CV	Steroid treatment did not significantly

Sr No	Study	Location	Study Design	Population	Sample Size	Intervention	Comparison	Outcomes	Results
			Trial					hospitalization, CV death or HF hospitalization, All-cause death, CV death, HF hospitalization	lower the incidence of the primary composite outcome of cardiovascular death, aborted cardiac arrest, or hospitalization for heart failure management in patients with heart failure and a preserved ejection fraction.
12	Yamamoto et al 2013 [27]	Japan	Randomised Controlled Trial	HFpEF	245	Carvedilol	Placebo	cardiovascular death and unplanned hospitalization for heart failure	Overall, the prognosis of HFPEF patients was not improved by carvedilol; however, the standard dosage—rather than the low dose—may be prescribed. This could make it easier to conduct additional research.
13	Park et al 2016 [28]	South Korea	Randomised Controlled Trial	older patients with HFpEF	-	nebivolol and carvedilol	Placebo	baseline Chracteristics	The study's findings will offer insights into the best β-Blocker to use in the treatment of patients diagnosed

Sr No	Study	Location	Study Design	Population	Sample Size	Intervention	Comparison	Outcomes	Results
									with HF with preserved EF.
14	Cleland et al 2006 [29]	UK	Randomised Controlled Trial	Chronic HFpEF	850	Perindopril	Placebo	all cause death, hospitalization, CV death	During the first year, there were improvements in symptoms, increased ability to exercise, and fewer heart failure hospitalizations. observed on perindopril, when the majority of patients were receiving their prescribed treatment, indicating that it might be advantageous for this particular patient group.
15	Parthasarathy et al 2009 [30]	UK	Randomised Controlled Trial	symptomatic HFpEF	152	valsartan	Placebo	peak VO2 and percentage of predicted peak VO2	In this group of patients, who were primarily symptomatic HFPEF patients with well-controlled hypertension, adding valsartan did not result in longer exercise sessions after 14

Sr No	Study	Location	Study Design	Population	Sample Size	Intervention	Comparison	Outcomes	Results
									weeks.
16	Ahmed et al 2006 [31]	USA	Randomised Controlled Trial	Heart Failure	5548	Digoxin	Placebo	all cause mortality, CV mortality, hospitalization,	Digoxin, even in patients with diastolic HF, lowers hospitalization and death rates Digoxin lowers hospitalizations for heart failure at higher SDC, but it has no effect on mortality or hospitalizations for other causes.
17	Mulder et al 2012 [32]	Netherlands	Randomised Controlled Trial	elderly patients with heart failure and atrial fibrillation	2128	Nebivolol	Placebo	All cause mortality, CV mortality, Hospitalization	Nebivolol also had a lower impact on cardiovascular hospitalizations and all-cause mortality in AF patients.
18	Mentz et al 2023 [33]	USA	Randomised Controlled Trial	Patients With Mildly Reduced or Preserved Ejection Fraction and Worsening Heart Failure	466	sacubitril/valsartan	Placebo	CV death, Recurrent hospitalisation, heart failure	Sacubitril/valsartan, although causing more symptomatic hypotension, resulted in a greater reduction in plasma NT-proBNP levels and was associated with a clinical benefit compared with valsartan alone

Sr No	Study	Location	Study Design	Population	Sample Size	Intervention	Comparison	Outcomes	Results
									among patients whose EF >40% stabilized after WHF.
19	Butt et al 2022 [34]	USA	Randomised Controlled Trial	Patients With HFpEF	4795	sacubitril/valsartan	Placebo	All cause death or CV hospitalization, CV death or HF hospitalization, All-cause death, CV death, HF hospitalization	Sacubitril/valsartan appeared to show a larger reduction in the primary endpoint with increasing frailty when compared to valsartan.
20	Kitzman et al 2020 [35]	USA	Randomised Controlled Trial	Older Patients With HFpEF	71	Enalapril	Placebo	Blood Pressure, LV function	Enalapril did not increase tolerance to physical activity.
21	Tsujimoto et al 2020 [36]	Japan	Randomised Controlled Trial	HFpEF With Resistant Hypertension	2437	Spironolactone	Placebo	All cause death or CV hospitalization, CV death or HF hospitalization, All-cause death, CV death, HF hospitalization	Spironolactone is a good adjunct to HFpEF therapy.

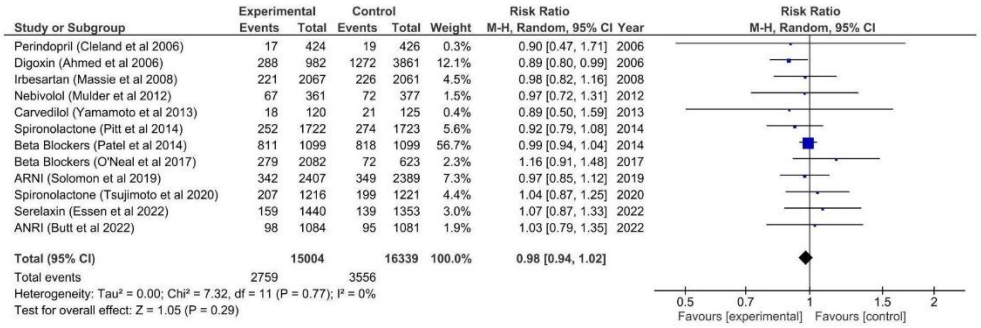

Fig 3. Forest Plot of All-cause Mortality. [17,19,20,21,24,26,27,29,31,32,34,36]

Fig. 4. Forest Plot of Cardiovascular Mortality. [19,21,24,26,27,29,31,32,34,36]

Fig. 5. Forest Plot of Hospitalization. [19,20,21],24,26,27,29,31,32,34,36]

Fig. 6. Forest Plot of Stroke. [17,26,36]

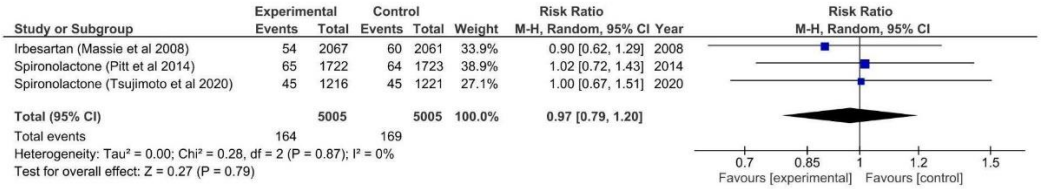

Fig. 7. Forest Plot of Myocardial Infarction. [17,26,36]

Cardiovascular Mortality: Cardiovascular Mortality was the primary outcome of this study. It is a dichotomous variable and Events and Totals were extracted for the experimental as well as control groups of each primary study. Random effects model is used to calculate Risk Ratio. Different drugs from B blockers [19], Serelaxin [21], ARNI [24], Spironolactone [26], Carvedilol [27], Perindopril [29], Digoxin [31], Nebivolol [32], ANRI [34], and Spironolactone [36]. The overall RR was found to be 0.95 [0.89, 1.03]. (Fig. 4).

Hospitalization: Hospitalization was one of the primary outcomes of this study. It is a dichotomous variable and Events and Totals were extracted for the experimental as well as control groups of each primary study. Different drugs from B blockers [19], B blocker [20], Serelaxin [21], ARNI [24], Spironolactone [26], Carvedilol [27], Perindopril [29], Digoxin [31], Nebivolol [32], ANRI [34], and Spironolactone [36]. The overall RR was found to be 1.00 [0.93, 1.07]. (Fig. 5)

Stroke: Stroke was one of the secondary outcomes of this study. It is a dichotomous variable and Events and Totals were extracted for the experimental as well as control groups of each primary study. Different drugs from Irbesartan [17], Spironolactone [26], and Spironolactone [36]. The overall RR was found to be 1.01 [0.82, 1.24]. (Fig. 6)

Myocardial Infarction: Myocardial Infarction was one of the secondary outcomes of this study. It is a dichotomous variable and Events and Totals were extracted for the experimental as well as control groups of each primary study. Different drugs from Irbesartan [17], Spironolactone (Pitt et al 2014) [26], and Spironolactone [36]. The overall RR was found to be 0.97 [0.79, 1.20]. (Fig. 7)

4. DISCUSSION

After careful analysis, we found that only beta-blockers and angiotensin-converting enzyme (ACE) inhibitors had a significant effect in HFPEF patients These data highlight the potential therapeutic benefits of beta blockers and ACE inhibitors as mainstream therapy for HFpEF. However, it is important to remember that the ineffectiveness of other medical interventions highlights the challenges in developing appropriate treatments for this complex condition Our findings highlight the need for further research is conducted on new therapeutic strategies and unmet clinical needs in the treatment of HFpEF are highlighted. Furthermore, our study highlights the importance of individualized treatment plans and optimized management strategies to improve outcomes in HFpEF patients.

Only one of the three beta-blocker trials reviewed showed a statistically significant reduction in spontaneous mortality. In this experiment, it is most likely that the increase in events had a significant effect on the overall results. Neither of the two large randomized controlled trials (RCTs) had sufficient power to detect an effect on mortality but found neutral results [20]. The observed effect of beta blockade on mortality suggests a favorable outcome. Previous meta-analyses of observational and pooled research have consistently found comparable advantages. However, only one of the three beta-blocker trials reviewed showed a statistically significant reduction in spontaneous mortality. In this experiment, it is most likely that the increase in events had a significant effect on the overall results. Although none of the large randomized controlled trials (RCTs) had adequate power to detect effects on mortality, the results were neutral.

Piadlo et al 2023 discovered that the complex pathophysiology of HFpEF includes comorbidity-related systemic changes. Its diagnosis is aided by streamlined diagnostic pathways that direct inconclusive cases to specialized facilities. Because of its increasing prevalence, HFpEF—which affects 50% of HF cases—represents the

greatest unmet need in cardiology. Given the similar outcomes of HFrEF, early intervention is critical to preventing mortality and morbidity. 50% of patients have five or more comorbidities, indicating that multimorbidity is widespread. While diuretic therapy and symptom relief have traditionally been the mainstays of management, new RCTs show that SGLT2 inhibitors—specifically, EMPEROR-Preserved and DELIVER—are effective in improving patient-reported outcomes and lowering the rate of heart failure hospitalizations and cardiovascular deaths [37].

In fact, among patients with HFmrEF (heart failure with mildly reduced ejection fraction), the post-hoc analysis of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity study (CHARM-Preserved) showed a significant 24% reduction in cardiovascular death and time to first heart failure hospitalization [38]. Patients with LV ejection fractions <50% showed greater potential efficacy of spironolactone in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial compared to patients with LV ejection fractions ≥60%. These findings suggest that treatment responses for heart failure patients can be differentiated based on LV ejection fraction subgroups [39].

Zheng et al. (2018) found that beta-blockers significantly reduced all-cause and cardiovascular mortality in trials involving patients with HFpEF, defined as an LV ejection fraction of less than 40%, similar to our SRMA findings. The reductions were found to be 22% and 25%, respectively. However, there was no apparent effect of ACE inhibitors and ARBs on this outcome. Furthermore, these treatments were found to have little effect on functional life and quality of life outcomes [40].

The methodology used in this study has some limitations that should be considered. To begin with, the inclusion of some studies may be biased, affecting the integrity and reliability of the findings. Various factors such as flawed study design, inadequate blinding, and selective reporting of outcomes may introduce bias and distort the overall results.

Second, as the definition of heart failure preserved ejection fraction (HFpEF) evolves over time, there may be differences among included trials Changes in study populations may be due to variability occurring in the form of assessment criteria and patient characteristics, affecting the overall findings.

Third, studies looking at various supplements introduce potential confounders that could affect the results of the meta-analysis. Drugs classified as "other" include a wide variety of drugs, including digoxin, calcium channel blockers, and vasodilators, each with a different mechanism of action These treatment regimens can make it difficult to determine which decrease the outcome and increase the variability in treatment response. Furthermore, this study is subject to the usual limitations of meta-analysis. These include limitations in data reporting and availability, publication bias, and the possibility of residual confounding even after controlling for covariates

5. CONCLUSION

Our findings suggest that patients with heart failure and preserved ejection fraction may have a significantly lower mortality rate when taking beta blockers and ACE inhibitors. However, due to limitations such as high-risk bias in some studies and heterogeneity in the drug classes studied, additional research is required to validate these findings. Filling in these gaps will be critical for improving treatment plans and HFpEF patient outcomes.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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