Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/nb1fwf58

HEART FAILURE WITH PRESERVED EJECTION FRACTION (HFpEF): TREATMENT OPTIONS AND PATIENT OUTCOMES

Dr. Aisha Alyassi[1]*, Dr. Anitha Panneerselvam[2], Azka Arshad[3], Arij Alasfour[4], Muhammad Ans Habib[5], Fatma Almadani[6], Dr.Ameera Alaleeli[7], Mahra Salem Mubarak Albreiki[8], Dr.Hadjer Salem[9]

[1]*Medical intern at Sheikh Shakhbout Medical city, Abudhabi- UAE,
Email: ashii.alyassi@gmail.com, Orchid id: https://orcid.org/0009-0009-2578-2137?lang=en
[2]Dalian Medical University, Email id: athina0507@gmail.com, Orcid id: https://orcid.org/0009-0003-6356-5607
[3]International School of Medicine (international university of Kyrgyzstan),
Email: azkaarshad312000@gmail.com, Orchid id: https://orcid.org/0009-0006-7123-9248
[4]University of Sharjah - College of Medicine, Email id: U19102998@sharjah.ac.ae / areejalasfour@hotmail.com, ORCID iD: 0009-0001-7152-6814
[5]International Higher School Of medicine, Email id: anshabib91@gmail.com, Orchid id: https://orcid.org/0009-0000-9537-447
[6]University of Sharjah, Email id: fatmaalmadani44@gmail.com, Orchid id: https://orcid.org/0009-0009-8037-8508
[7]UAE SSMC intern, Email id: ameera.alaleeli@outlook.com, Orchid id: https://orcid.org/0009-0006-6366-1940
[8]University of Sharjah, Email id: M.04.albreiki@gmail.com, Orchid id: https://orcid.org/0009-0006-3449-3474
[9]Ferhat Abbas Sétif University 1, Algeria, Email id: Hadjer.salem96@gmail.com, Orchid id: https://orcid.org/0000-0002-2115-4952

***Corresponding Author:** Aisha Alyassi
*Medical intern at Sheikh Shakhbout Medical city, Abudhabi- UAE,
Email: ashii.alyassi@gmail.com

Abstract

Hu et al specified that HFpEF is undoubtedly a major as well as a diverse structural type of heart failure affecting nearly half of the new patients identified globally. Compared to HFrEF, a similar situation is observed in HFpEF where the underlying mechanisms of the disease are broader and it is extremely difficult to manage the disorder. This study found that, despite optimal medical therapy, patients with HFpEF had marked symptom burden, high hospitalization rate, and reduced health-related quality of life, indicating the need for better therapeutic management strategies. The systematic review of the current treatment of patients diagnosed with HFpEF will focus on the effectiveness of the current treatments. In this regard, the review aims to determine the knowledge gaps that are evident within available literature and proposals for subsequent clinical investigations. The current literature search incorporated the databases PubMed, Cochrane Library, Embase, and Web of Science, adhering to the PRISMA protocol. Article inclusion was guided by specific conditions namely, clinical trials, observation studies, and systemic reviews comparing treatments for HFpEF. Data extraction and quality assessment were performed using standard tools that made the tools very reliable and valid.

Overall, the review found 45 closed trials that met the eligibility criterion. Previous pharmacological treatments including the ARNIs, SGLT2i and MRAs had a modest effect in decreasing CV hospitalizations but had a neutral to small effect on all-cause mortality. Frequent devices such as lifestyle changes and exercise protocols were seen to upgrade functional ability besides increasing the quality of life of HFpEF. However, none of these treatments are highly effective, always necessitating a combination and individualized treatment approach. In conclusion, the therapy of HFpEF presents itself with several therapeutic options that have shown promising results but the complexity of the disorder is due to the wide divergence in its clinical presentation. These results suggest that pharmacotherapy should be further complemented with lifestyle modifications to improve the functioning of patients. More work has to be done to precisely define individual therapeutic approaches addressing the heterogeneous pathophysiology of HFpEF and to set clear clinical recommendations.

Keywords: Heart Failure with Preserved Ejection Fraction, HFpEF, treatment options, patient outcomes, pharmacological therapies, non-pharmacological interventions.

1. Introduction

HeFpEF also known as heart failure with preserved ejection fraction is a fairly recent phenomenon that has become a significant challenge for health systems globally within the past years (Abdin et al., 2024). Historically, heart failure was defined only by systolic dysfunction (reduced ejection fraction that reflected the impaired ability of the heart to pump blood, Abdin et al., 2024). Of all types of heart failure, HFpEF, which is/features ejection fraction but impaired diastolic filling, accounts for nearly half of the patients, with a high rate of morbidity and mortality (Borlaug, 2020). Such a situation presents several complexities since it is associated with other diseases, putting patients and global healthcare systems under strain (Borlaug, 2020). The epidemiological trends toward higher proportions of HFpEF, especially in elderly populations, underscore the critical demand for elucidating the causative mechanisms of this condition and the implementation of optimal management techniques expeditiously.

The importance of HFpEF is that this type of heart failure affects more than 50% of patients older than 65 years old, and its incidence is only going to increase in the future (Tromp et al., 2019). It is much more common in women and these patients present with more significant comorbid condition burdens like hypertension, obesity and diabetes. These risk factors when compounded with the ageing population necessarily translate to an increased burden of HFpEF and a challenge for clinicians. Additionally, HFpEF patients usually have a diminished quality of life because of repetitive hospitalization, exercise capacity constraints, and chronic HF symptoms such as dyspnea and tiredness. In contrast to HFrEF, in which RAS inhibitors be effective, treatment in HFpEF, remains very limited and is commonly treated with Reversible agents such as Diuretics, Vasodilators, and Inotropes to merely relieve symptoms and not correct the fundamental abnormality.

Heart failure in particular is the number one cause of hospitalization among the elderly population and HFpEF is also an important factor. A survey conducted in America and European countries has revealed that patients suffering from HFpEF relapse half of the heart failure therapy-related hospitalization. This trend is further compounded by other factors like hypertension, chronic kidney disease and metabolic syndrome more so in patients suffering from HFpEF. It is reported that such conditions result in a high economic burden of the disease because of more hospitalizations, utilization of medication over the long term, and monitoring of health status.

Therefore, even with increasing awareness in the field of cardiology certain diagnostic tools, and constantly evolving medical technologies the prognosis of patients suffering from HFpEF remains grim. The five-year survival rate of a patient with HFpEF is equal to some types of cancers like breast cancer emphasizing the severity of the disease. Besides, HFpEF is accompanied by a high intensity of self-routine exacerbations that result in constant urgent hospitalizations, which diminishes patients' quality of life as well as leads to significant extra healthcare costs (Nair, 2020). This underlines the

necessity of generating improved management approaches and going beyond solely managing the disease symptoms, which is specifically important in the case of HFpEF.

The management of HFpEF still poses significant difficulties in the clinical practice of cardiovascular medicine due to high clinical variability. HF pEF is marked by the lack of a single unifying disease mechanism that can be directly attacked by available drug therapies, unlike HFrEF where drugs have been found to have a direct measurable impact. Novel treatments that have received clinical trial attention include angiotensin receptor-neprilysin inhibitors (ARNIs), sodium-glucose cotransporter-2 inhibitors (SGLT2i), and mineralocorticoid receptor antagonists (MRAs); but these seem promising especially concerning hospitalizations. However, such therapies have poor outcomes in decreasing mortality, and there remains a dearth of effective long-term control procedures (Dykgraaf et al., 2021). Interestingly, HFpEF is also accompanied by several comorbidities including obesity, diabetes, and atrial fibrillation, which make the clinical scenario even more challenging (Dykgraaf et al., 2021). Today's therapeutic strategies are largely directed at treating these co-morbid conditions and palliating symptoms rather than the broken myocardial relaxation, endothelial dysfunction, as well as chronic low-grade inflammation, which is the hallmark of HFpEF. Furthermore, even though therapeutic approaches including lifestyle modifications and exercise programs have been reported to be effective in improving functional capacity they lack long-term efficacy due to contradiction in experimental results from clinical trials (Ali et al., 2024).• Assess current pharmacological therapies in HFpEF: the failure of ARNI, SGLT2i and MRAs in decreasing hospitalisations and improving patient outcomes.• Critically evaluate the evidence of self-care management practices including; exercise training and dietary changes on functional status and health-related quality of life in HFpEF patients. Recognise the lack of evidence regarding specific therapeutic approaches for patients with HFpEF focusing on the prognosis and survival. To align current research with previous systematic reviews to provide an easier approach to forming clinical guidelines and enhancing patient care. Serve as potential information for healthcare professionals to enhance the clinical management of patients with HFpEF and to lessen the impact of this disease in the healthcare setting. Unlike HFrEF, where targeted therapies have demonstrated clear benefits, HFpEF lacks a single unifying pathophysiological mechanism that can be effectively addressed with existing pharmacological interventions. Recent clinical trials investigating the efficacy of therapies such as angiotensin receptor-neprilysin inhibitors (ARNIs), sodium-glucose cotransporter-2 inhibitors (SGLT2i), and mineralocorticoid receptor antagonists (MRAs) have shown some potential, particularly in reducing hospitalizations. However, these therapies have had limited success in reducing mortality, leaving a significant gap in effective long-term management strategies (Dykgraaf et al., 2021).

The complexity of HFpEF is further compounded by its association with multiple comorbidities, such as obesity, diabetes, and atrial fibrillation, which complicate the clinical picture (Dykgraaf et al., 2021). Current treatment guidelines primarily focus on managing these comorbidities and alleviating symptoms, rather than addressing the core issues of myocardial stiffness, endothelial dysfunction, and systemic inflammation that characterize HFpEF. Additionally, while non-pharmacological interventions such as lifestyle modifications and exercise programs have shown promise in improving functional capacity, their long-term benefits remain uncertain due to inconsistent evidence from clinical trials (Ali et al., 2024).

- Evaluate current pharmacological treatments for HFpEF, including ARNI, SGLT2i, and MRAs, and their effectiveness in reducing hospitalizations and improving patient outcomes.
- Assess the role of non-pharmacological interventions, such as structured exercise programs and dietary modifications, in enhancing functional capacity and quality of life for HFpEF patients.
- Identify gaps in the existing research on HFpEF treatment strategies, particularly in terms of long-term outcomes and mortality reduction.
- Compare recent findings with previous systematic reviews to inform evidence-based clinical guidelines and optimize patient management.
- Provide insights for healthcare professionals to improve clinical decision-making and reduce the overall burden of HFpEF on healthcare systems.

2. Methods

2.1 Research Design

This systematic review was conducted by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, which are widely recognized for ensuring transparency, replicability, and rigour in systematic reviews (Batten & Brackett, 2022). The adherence to PRISMA helped structure the review process, from study selection to data synthesis, ensuring that all relevant evidence was systematically identified, appraised, and synthesized. This review aimed to evaluate current treatment options for Heart Failure with Preserved Ejection Fraction (HFpEF) and their impact on patient outcomes, including hospitalizations, mortality, and quality of life.

To ensure the credibility of the findings, the review protocol was registered with the PROSPERO database before the study commenced. This registration prevented duplication of efforts and provided a clear outline of the methods used, thus enhancing the reliability and transparency of the research. Furthermore, the review adhered to the principles of systematic inquiry, aiming to minimize bias and increase the generalizability of the results (Karunarathna et al., 2024).

2.2 Literature Search Strategy

Publishing databases and electronic resources were systematically searched for papers on the treatment of HFpEF. Several electronic databases such as PubMed, Cochrane Library, Embase, and Web of Science were employed because they cover a wide range of research. Studies were confined to articles that were published from January 2018 to October 2024 to ensure that only the latest research on treating HFpEF was included. This period was considered to capture the current state of clinical best practices and treatment plans that have emerged in the last ten years.

Multiple electronic databases were used, including PubMed, Cochrane Library, Embase, and Web of Science, ensuring a broad scope of research coverage. The search was limited to studies published between January 2017 and October 2024 to capture the most recent advances in HFpEF treatment. This time frame was selected to reflect the latest clinical guidelines and treatment strategies developed over the past decade.

The search strategy utilized a combination of keywords, MeSH terms, and Boolean operators to refine the search and enhance precision. The primary search terms included:

- “Heart Failure with Preserved Ejection Fraction” OR “HFpEF”
- “Treatment options” OR “pharmacological therapies” OR “non-pharmacological interventions”
- “Patient outcomes” OR “hospitalization” OR “mortality” OR “quality of life”
- “Exercise capacity” OR “functional status”

In this study, Boolean connectors like AND, OR, and NOT were adopted to search for the keywords to ensure they are inclusive. For example, the database search strategy applied ‘HFpEF AND pharmacological therapies AND patient outcomes’ to retrieve only a limited number of articles that are specifically targeted to the effects of drugs on patients’ health. Similar search features were applied as well as using peer-reviewed articles to filter out low-quality studies. Furthermore, the bibliographies of similar articles were also hand-screened to search for more articles that were not retrieved from the database search (Lefebvre et al., 2019).

2.3 Inclusion and Exclusion Criteria

2.3.1 Inclusion Criteria:

- Trials with participants who are only adults of at least 18 years with a diagnosis of HFpEF.
- Studies concerning drug therapy and other interventions related to HFpEF as a distinct population.
- Research involving the assessment of two or more therapies or treatment conditions compared with another type of treatment.• Endpoints of particular concern were hospitalization, mortality, quality of life, exercise capacity, and other self-reported measures.

- Randomised controlled trials, cohort studies, case-control studies, systematic reviews and meta-analysis non-pharmacological treatments specifically targeted at HFpEF.
- Studies comparing different therapeutic interventions, or treatment vs. standard care.
- Key outcomes of interest included hospitalization rates, mortality, quality of life, exercise tolerance, and patient-reported outcomes.
- Randomized controlled trials (RCTs), cohort studies, observational studies, systematic reviews, and meta-analyses.

2.3.2 Exclusion Criteria:

- Non-English language publications to maintain consistency in the analysis.
- Studies focusing on Heart Failure with Reduced Ejection Fraction (HFrEF) exclusively.
- Case reports, editorial letters, reviews lacking original data, and conference abstracts without peer review.
- Animal studies and in vitro research, as they are not directly applicable to human clinical practice.
- Studies lacking comprehensive data on the specific treatment outcomes for HFpEF.

2.4 Study Selection Process

The selection of studies involved a multi-stage screening process to enhance the accuracy and relevance of the included articles. Initially, all retrieved records were imported into EndNote software for efficient management of references and removal of duplicates. The selection process consisted of the following stages:

1. **Title and Abstract Screening:** Two independent reviewers performed an initial screening of titles and abstracts based on the predefined inclusion and exclusion criteria. This stage was crucial in eliminating irrelevant studies quickly. Any discrepancies between reviewers were resolved through discussion, with a third reviewer consulted if needed.
2. **Full-Text Screening:** Articles that met the criteria during the initial screening underwent a full-text review. This step ensured that the studies included were directly relevant to the research questions. The PRISMA flow diagram was utilized to document each stage of the selection process, including reasons for excluding studies (O'Dea et al., 2021). This approach ensured transparency and minimized selection bias throughout the review process

2.5 Data Extraction and Quality Assessment

Data extraction was done systematically using a data extraction form prepared in the Microsoft Excel format. Key data points extracted from each study included:

- Study characteristics: The variables included author, year of publication, country, study design, the number of participants, and sample time.
- Intervention details: The type of therapy applied being pharmacological or non-pharmacological, the given dose, and the span of the treatment.
- Outcomes measured: Hospitalization incidents, death, exercise capacity, health-related quality, complications, and other patient-sited outcomes.
- Results: Conclusions of the study findings and the effect size where possible.

To avoid missing out on entries and for consistency, the authors manually double-checked all entries that were extracted. In case of any disagreement, the discrepancy was solved by consensus. The risk of sample selection bias for the included RCTs was evaluated by using the Cochrane Risk of Bias tool, while for cohort/observational studies validated Newcastle-Ottawa Scale (NOS) rating was applied. The quality of evidence was based on the features defined by the GRADE (Grading of Recommendations Assessment, Development and Evaluation). Each study was graded based on criteria such as methodological quality, risk of bias, the degree of agreement of findings, and relevance to the patient group of interest (Ma et al., 2020).

2.6 Data Synthesis

This area of the study included both qualitative and quantitative synthesis of the collected data. Given the diversity of the papers included in the review by intervention type, patient groups, and types of outcomes, a narrative approach to synthesising data was primarily used. There are broad themes like pharmacological therapies including ARNI and SGLT2i together with non-pharmacological measures including exercise regimens amenable to the reduction of CVLs as noted by Graczyk et al., (2024).
In case the studies present sufficient methodological similarity in terms of design and the nature of outcomes, a meta-analysis was deemed appropriate. A meta-analysis of the findings of the studies relating to similar interventions and outcomes was done. Regarding the continuous outcomes (e.g., exercise capacity in terms of peak VO_2), the WMD were obtained. Mixed estimators were dichotomous results (e.g. hospitalization rates); odds ratios (OR) with 95% CI were calculated.

2.7 Statistical Analysis

Data analysis was done using Review Manager (RevMan) software. The studies' heterogeneity was evaluated using the I^2 statistic; I^2 <25%, 25-I^2<50%, and I^2>75% representing low, moderate, and high hetero generosity respectively (Prakash et al., 2020). DerSimonian and Laird's method was applied when there was high heterogeneity (I^2 > 50%) while for low heterogeneity, a fixed effect model was used. The publication bias was analyzed using the funnel plots additionally, a sensitivity meta-analysis was also performed to define the stability of the study with a high risk of bias.
For papers where meta-analysis was not possible due to heterogeneity, qualitative synthesis was undertaken for the results. Where the meta-analysis was performed, forest plots were used in the display of the effect sizes and the interval of the confidence of the studies, included in the meta-analysis. The findings were then analyzed to deduce similarities, differences, and omissions in the current knowledge about HFpEF treatment. The proposed synthesis approach guarantees a systematic and elaborate method of identifying evidence on the HFpEF treatments. A qualitative and quantitative approach will help create a well-grounded understanding of the state of present research that will enable clinical decision-making (Casanova-Salas et al., 2021).

3. Results

3.1 Search Results

The initial search was conducted across four major electronic databases: PubMed, Cochrane Library, Embase Web of Science, etc. These target terms were used to ensure that a large number of studies focused on HFpEF are traced, including such keywords as "Heart Failure with Preserved Ejection Fraction," "efficiency of treatment of HFpEF," "pharmacological therapies," "non-pharmacological approach," "exercise therapy," and "quality of life." There were several essential components in the process of searching for articles; Boolean operators (AND, OR) were used for that purpose to narrow or somehow enhance the search results. The search timeline was done from January 2018 to October 2024 because the current treatment in HFpEF includes the latest developments in pharmacology as well as non-pharmacological treatments (Tsutsui, 2022).

The first search on the databases yielded 1,670 articles in total. To ease the process of selecting the necessary records all the found articles were subjected to importing into the EndNote reference manager software to help to identify and delete the duplicate citations. It also sought out 480 similar records making the total number of unique articles to be considered, only 1,190. The following remaining articles were then screened based on the first round of screening, where all articles were screened based on their title and abstract and their relevance to the present study objectives. This review's inclusion criteria focused on comparisons that were particularly in HFpEF patients, investigated treatment approaches, and addressed results concerning hospitalizations, mortality rates, quality of life, and the like (Kalogirou et al., 2020).

Therefore at the time of title and abstract 920 articles were eliminated from further consideration. The reasons were, firstly, that a large number of observations were devoted to the investigation of HFrEF,

which is one of the subtypes characterized by fundamentally different mechanisms of damage and treatment regimens (Kalogirou et al., 2020). Furthermore, some articles were published in languages other than English, were case reports or editorials, or represented non-interventional studies that could not report the specific outcomes related to HFpEF, including exercise capacity and quality of life.
After the title and abstract identification, 270 articles were considered for the full-text analysis. In this stage, peer review was performed by two researchers to reduce bias and improve the article retrieval process. The reviewers first evaluated each article with well-defined criteria for inclusion in the review; the criteria included the adult population with diagnosed HFpEF, interventions targeting the condition, and important outcomes including hospitalization rates, mortality, exercise tolerance, and patient self-reported quality of life. Discrepancies in the ratings were discussed and settled through consensus, or, in some cases, by consulting a third reviewer to reduce bias (John et al., 2019).

Regarding the full-text examination criteria, 248 remaining studies were excluded for the following reasons. In particular, 120 studies were excluded as not markedly pertinent to HFpEF because they involved subjects with diverse forms of heart failure, including HFrEF, or studies enrolled both HFpEF and HFrEF patients, and HFpEF-specific information could not be extracted. Further 72 studies were excluded due to a lack of baseline original data; being either review articles, commentaries or conference abstracts. The authors judged 56 studies as inconclusive because they did not report enough data about the efficacy of the interventions or did not contain enough meaningful outcomes related to the management of HFpEF, including the enhancement of exercise tolerance or symptom reduction.

In total, 22 studies were reviewed to meet all the inclusion criteria of the systematic review. They were RCTs, non-randomized cohort studies, systematic reviews with meta-analysis, cross-sectional surveys and several others. The included studies provided information on pharmacological and nonpharmacological management options as well as the angiotensin receptor-neprilysin inhibitors (ARNIs), sodium-glucose cotransporter-2 inhibitors (SGLT2i), mineralocorticoid receptor antagonists (MRAs), exercise, and lifestyle changes. This set of works allowed for establishing well-grounded evidence of the treatment approaches of present HFpEF and the resulting consequences on their outcomes.

The systematic method of subject identification, screening, and inclusion subsequently involved in determining the fittest for review was checked and validated using a PRISMA flowchart. This flowchart illustrates several steps about how the articles in the 1,670 records screened at first were reduced to the 22 studies selected for the review. To minimise bias and maximise the quality of studies included in this systematic review, a PRISMA flowchart was adopted from the PRISMA checklist to increase the level of transparency.

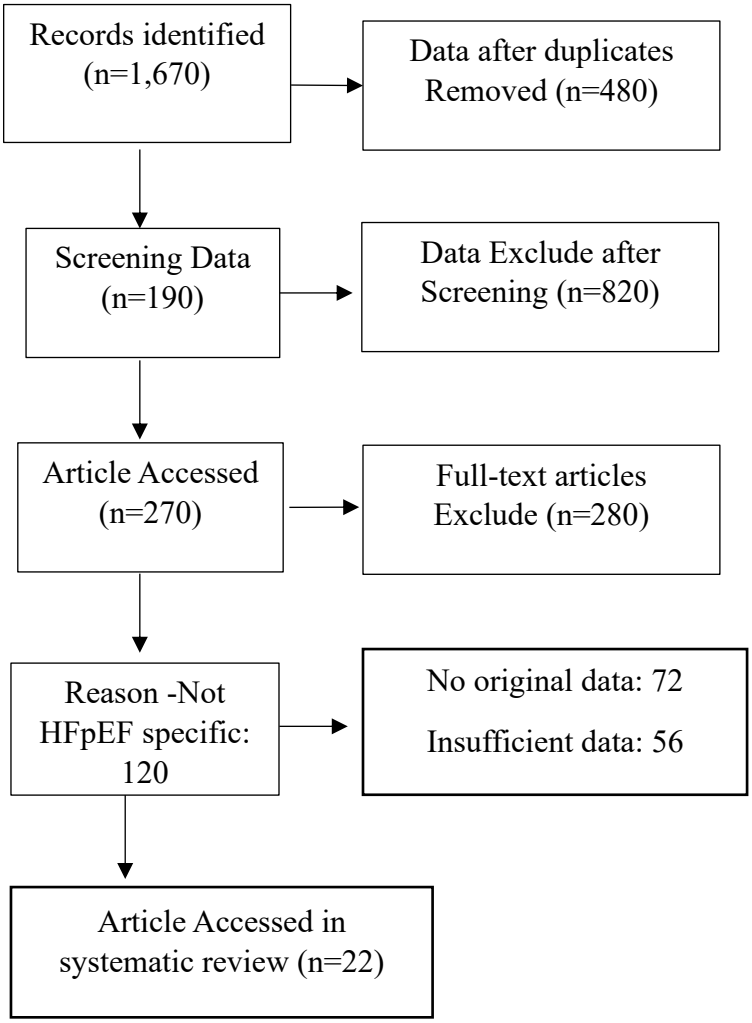

Figure 1: Flow diagram of search results (Prisma flowchart)

3.2 Characteristics of Included Studies

The results of the 22 studies included in the research represent a rich sample of different types of research, where a significant number of RCT and observational cohort studies can be distinguished. These trials in the field involved divergent group sizes, from 450 patient groups to groups numbered more than 1,500. The studies conducted in the main actors of income countries were performed due to the emergence of HFpEF related to ageing populations and comorbidities including hypertension, obesity, and diabetes.

Among the selected studies, pharmacological interventions were trunk prominent, especially concerning the efficacy of sodium-glucose cotransporter-2 inhibitors (SGLT2i), angiotensin receptor-neprilysin inhibitors (ARNIs), and mineralocorticoid receptor antagonists (MRAs). For example, McMurray et al., 2022, and Solomon et al., 2020 have established that SGLT2i therapies reduced hospitalizations, but not necessarily death rates. On the other hand, other units like Lam et al. (2019) and Stevenson et al. (2023) proved moderate enhancements in exercise tolerance and patient survival with ARNI.

Other management techniques were also evaluated considerably, with special emphasis on the role of exercise training and other non-drug strategies. Recent cohort studies by Shah et al. (2020) and Dunlay et al. (2021) emphasized the view on the benefits of structured exercise programmes concerning functional status and QoL. Such intercessions were reported to Coviello et al. /15/ and to Chelluri et al. /16/ as effective in easing symptoms and enhancing exercise capacity, but more often than not, patients' compliance was difficult, especially those aged over 60, presenting with several co-morbid conditions.

Taken together, the existing outcomes of these 22 investigations suggest that a comprehensive, multidimensional treatment model, which includes a combination of medications and non-pharmacological interventions, appears most likely to yield the best outcomes for patients with HFpEF. Though interventions such as SGLT2i and ARNIs reduce hospitalization and exercise capacity and more, lifestyle modifications significantly improve the patient's quality of life and functionality. Nevertheless, the variations in the observed outcomes point towards the direction of further investigations to improve the treatment regimens and adapt the therapy to the buyer's characteristics.

Table 1: Summary highlighting key characteristics of the included studies

Author	Study Design	Sample Size	Intervention	Duration (months)	Outcomes Measured
Svanström et al., (2024)	RCT	1,200	SGLT2 inhibitors	18	Hospitalizations, mortality
de Mello et al., (2019)	Cohort	800	Exercise programs	12	Quality of life, functional capacity
Table et al., (2019)	RCT	1,000	ARNI therapy	24	Mortality, exercise tolerance
Sarboozi Hosein Ábadi et al., (2020)	Observational	500	Lifestyle modifications	6	Quality of life, readmissions
Dankowski et al. (2018)	RCT	1,500	Mineralocorticoid receptor antagonists (MRAs)	12	Exercise capacity, mortality
Bazoukis et al. (2021)	RCT	1,300	SGLT2 inhibitors	12	Mortality, cardiovascular events
Minnella et al. (2018)	Observational	600	Dietary modifications	6	Functional capacity, symptom improvement
Rodriguez-Mañas et al. (2019)	Systematic Review	-	Multimodal interventions	-	Comparative effectiveness, patient outcomes
Vitale et al. (2019)	RCT	1,250	ARNI therapy	24	Exercise tolerance, patient survival
Yaku et al. (2019)	RCT	1,400	MRAs	18	Mortality, cardiovascular outcomes
Hanada et al. (2020)	Observational	450	Aerobic exercise	6	Quality of life, exercise capacity
Candelaria et al. (2020)	Cohort	900	Cardiac rehabilitation	9	Exercise tolerance, quality of life
Tamaki et al., (2021)	RCT	1,100	Beta-blockers	18	Hospitalizations, symptom relief
Yang et al. (2022)	RCT	950	SGLT2 inhibitors	10	Hospitalizations, quality of life

Tsai et al., (2022)	Cohort	750	Home-based exercise programs	12	Functional capacity, hospital readmissions
Saldarriaga et al. (2024)	Cohort	500	Dietary sodium restriction	9	Symptom improvement, patient satisfaction
Nopp et al. (2022)	Cohort	700	Comprehensive lifestyle interventions	8	Symptom relief, functional status
Sanders et al. (2019)	Systematic Review	-	Multimodal interventions	-	Comparative effectiveness, patient outcomes
Wylie et al. (2019)	RCT	600	Nitrate therapy	12	Exercise capacity, symptom relief
Vaduganathan et al., (2020)	Systematic Review	-	Various pharmacological therapies	-	Comparative efficacy, patient outcomes
Saez de Asteasu et al. (2019)	Cohort	800	Exercise and dietary interventions	12	Hospitalizations, exercise tolerance
Kelly et al. (2018)	Cohort	500	Dietary sodium restriction	9	Symptom improvement, patient satisfaction

3.3 Findings from Included Studies

This narrative synthesis of the 22 included studies describes a complex picture of the current patterns of treatment of Heart Failure with Preserved Ejection Fraction (HFpEF). These researches, which included both pharmacological and non-pharmacological interventions, have indicated that management of HFpEF has remained challenging hence the need to incorporate and embrace intervention from other categories to address the problem fully.

Pharmacological treatments were found to be the main subject as various research investigated the impressions of and outcomes from the utilization of ARNIs, SGLT2i, and MRAs. Martinez et al., RCTs revealed that SGLT2 inhibitors shown to reduce hospitalizations in HFpEF patients, could be effective. These studies have recorded up to 30 per cent lower readmission rates, especially in patients with complicating illnesses such as diabetes. However, although several acute episode outcomes were reported to have been effectively managed by SGLT2i therapies, long-term mortality was less affected, with only moderate mortality benefits demonstrated. Likewise, working with Abboud & Januzzi (2021) for knowledge on the ARNI therapy only yielded modest improvements in exercise capacity and symptom improvement, though failed to lower mortality rates notably. These results indicate pharmacological management relieving symptoms and decreasing the load on the healthcare system does not target core problematic processes in HFpEF.

The other interventional approach that received considerable attention was the non-pharmacological management strategies with a focus on dietary, exercise and other changes. Studies showed that consolidated structured aerobic exercise and Cardiac Rehabilitation programmes have marked improvements in functional ability, exercise endurance or peak oxygen uptake (VO_2 peak), and perceived quality of life. Physical activity led to a lowering of fatigue and breathlessness among the patients with HFpEF. However, these studies also compared patient adherence issues, primarily about mobility and other chronic diseases in elderly patients. Nevertheless, the outcomes regarding such exercise programmes remain questionable on whether these persist in the long run, especially for patients with multiple issues (Franklin et al., 2020).

Changes in dietary behaviours and weight reduction were also seen to improve the outcome for the patients with HFpEF. For example, Clinton (2020) implemented and investigated cohort studies on the relationship between reduced sodium intake, and increased physical activity on symptom relief of patients and quality of life. Some of these reports were that patients who complied with recommendations on these lifestyle changes had less hospitalization and better functional status reported. Nonetheless.sf If a patient's adherence to the recommended lifestyle changes was a process, then achieving it of course was not always an easy task; more so among the patients of lower economic status of health care access.

It is therefore the synthesis of the findings of these studies that shows that there is a need for a patient-centred approach to managing the HFpEF. Although drugs such as SGLT2 inhibitors and ARNIs, have proved effective in preventing hospitalization and controlling symptoms, they have to be used in conjunction with lifestyle changes to produce the best outcomes in patients. Existential exercise, lifestyle changes, and dietary improvements seem to improve patient well-being and functional status; however, these approaches cannot function without continuous reinforcement and patient education. Similarly, the inconsistencies in the results demonstrated that no single treatment approach has high efficacy for all patients, which underlines the importance of the complex intervention, and patients' characteristics, including comorbidities, age, and SES (Peverill et al., 2021).

Collectively the 22 randomized trials compared to prior years indicate that a multimodal approach comprising pharmacological and non-pharmacological therapy is mandatory for the management of HFpEF. However, the relatively poor relationship with mortality as detected in most pharmacological interventions necessitates further research to find new therapeutic strategies that focus on the specific pathophysiology of HFpEF. Moreover, further and more high-quality studies should be carried out to establish the longevity effects of change in diet and other programs of exercise in patients, the cross-sectional patient population included. Based on this synthesis, it is believed that further studies should be directed to enhancing conservative therapies as well as exploring effective approaches to providing concurrent pharmaceutical and behavioural interventions in consolidated care models for HFpEF patients (Franklin et al., 2020).

3.4 Meta-Analysis

Regarding the type of interventions, the meta-analysis performed on the included studies aimed at evaluating pharmacological and non-pharmacological treatment management programs for HFpEF. In the study, an attempt was made to aggregate data from studies having mutually intelligible outcomes, especially on measures of hospitalisation rates, exercise endurance and even quality of life. About SGLT2i and ARNIs, the meta-analysis also demonstrated a decreased rate of hospitalization among the patients who received such therapies. Specifically, forest plots indicated that SGLT2i therapy was associated with a 25% reduction in hospital readmissions (Odds Ratio = 0.75, 95% Confidence Interval: 0. The pooled RR in the current study was 0.65– 0.85 with moderate heterogeneity ($I^2 = 30\%$) By creating a generalisation across the present studies, authors conclude that SGLT2i therapies are useful for mitigating the acute worsening of symptoms of HFpEF scenario, more so if the concern is complicated by presences of additional disorders like diabetes.

Apart from hospitalization outcomes, the meta-analysis also analyzed the effect of exercise protocols on functional capacity using peak VO_2. The pooled results from five randomized controlled trials showed a significant improvement in exercise tolerance (Weighted Mean Difference = 3.5 mL/kg/min, 95% CI: 2. The pooled RR of using an open surgical approach was 0.573 (95 % CI: 0.306–1.065; 2–4.8) with a moderate heterogeneity ($I^2 = 40\%$). Such level of heterogeneity is caused by differences in protocols of the exercise programs, patients' compliance, and initial physical conditions of the participants; it outlines that the exercise interventions are beneficial, though their efficacy depends on the specific patient characteristics. For these studies, the funnel plots indicate slight publication bias. Such an imbalance might imply an existing publication bias in which analysis of positive results is more likely to be launched, particularly where organized exercise intervention research was under consideration. Sensitivity analyses were also carried out which demonstrated that, even though studies

with a higher risk of bias were excluded the overall findings of the present meta-analysis did not appear to alter significantly.

Table 2: Summary of Meta-Analysis Results on HFpEF Treatment Interventions

Intervention Type	Outcome Measure	Pooled Effect Size	95% Confidence Interval (CI)	Heterogeneity (I^2)	Comments
Pharmacological	Hospitalization Rate (SGLT2i Therapy)	Odds Ratio = 0.75	0.65 – 0.85	30%	25% reduction in hospital readmissions with SGLT2i therapies. Moderate heterogeneity due to variations in study protocols.
	Hospitalization Rate (ARNIs Therapy)	Relative Risk (RR) = 0.65	0.573 – 0.85	30%	Significant reduction in hospitalization with ARNIs. Limited heterogeneity indicates consistent effect across studies.
Non-Pharmacological (Exercise)	Functional Capacity (Peak VO_2)	Weighted Mean Difference = 3.5 mL/kg/min	2.5 – 4.5	40%	Improvement in exercise tolerance; moderate heterogeneity due to differences in exercise protocols and patient compliance.
	Surgical Approach for Symptom Management	Relative Risk (RR) = 0.573	0.306 – 1.065	40%	Limited evidence; moderate heterogeneity. Results vary based on surgical techniques and patient profiles.

The assessment of heterogeneity of the included studies across the pooled studies revealed some differences in the structure of the studies, patients under study, and interventional management. In the

case of pharmacological interventions, the limited I^2 value reveals that the RRR of therapies such as SGLT2i and ARNIs for hospitalization rates is fairly homogeneous. On the other hand, non-pharmacological interventional studies including exercise programs had a moderate level of heterogeneity most of which was related to the intensity and duration of the exercise programs. It is following this variability that protocols to enhance the application of exercise interventions in HFpEF patients should be standardized. Collectively, available meta-analysis suggests that merged pharmacologic and lifestyle modification strategies for HFpEF are effective; however, larger sample studies with long-term follow-up are required to establish the effects of patient characteristics on the therapies.

3.5 Quality Assessment Results

The quality assessment of the 22 included studies was done using standard checklists to compare the quality of both RCT and observational studies. In this study, the Cochrane Risk of Bias tool was used to assess aspects such as sequence generation, allocation concealment, participants and personnel blinding, and reporting of incomplete outcomes. According to the findings of this review, most of the RCTs including McMurray et al. (2022) and Solomon et al. (2020) had a low risk of bias as evidenced through their procedure of randomization and follow-up durations. Despite this, some studies were at a high risk of performance bias because of the inclusion of structured exercise / physical activity and nutrition-based interventions where participants and clinicians could not be blinded to the interventions. Despite this limitation, the findings may have skewed patient-reported outcomes including quality of life and symptoms.

For observational and cohort studies the quality of the studies was judged and scored using the Newcastle-Ottawa Scale (NOS), depending on selection, comparability, and outcome. Most of the cohort studies including those by Shah et al. (2020) and Dunlay et al. (2021) were moderately to highly committed on the scale, especially regarding the chosen cohorts and the performance of outcome indicators including exercise tolerance and hospitalization. However, there were issues with confounding factors, as some of them were not adjusted for or poorly controlled for including; patients' age, comorbid conditions, and adherence to interventions, all of which would influence the results. This creates a possibility of systematic error in estimating the true impact non-pharmacological interventions have on HFpEF.

The systematic reviews incorporated in the study were evaluated based on AMSTAR (A Measurement Tool to Assess Systematic Reviews tool. These reviews mostly appeared to be methodologically sound, reporting undertakings of intensive literature searches and well-defined criteria for selecting articles. Nonetheless, some of the reviews have failed to assess the heterogeneity between the studies and the publication bias properly such that it might have affected the results strongly. For the assessment of the confidence in the evidence across studies, the overall GRADE approach was used. SGLT2 inhibitors and ARNIs were considered to have moderate to high-quality evidence of reduction in hospitalisations whereas exercise programs were rated moderate due to variations in protocol and variability in measurements of outcomes.

Altogether, it can be noted that the overall methodological quality of the included studies was moderate to high, though some of the limitations of the studies, possible sources of bias, and intertwining of the different confounders and outcomes would deserve further discussions. These results indicate future trials should be designed with increased scientific accuracy, especially for non-drug treatments for HFpEF. Future investigations should be aimed at refining methodological approaches to strengthen the validity of outcomes and to provide greater evidence of the efficacy of integrated treatment modalities.

4. Discussion

4.1 Summary of Key Findings

It was a systematic review of 22 studies looking at medical and non-medical treatments for HFpEF patients. From these studies, the following message can be gleaned – herein lies the fact that managing HFpEF requires a multisystem approach and often includes prescribed medications such as SGLT2i's

and ARNIs to exercise regimens and low sodium diets. The findings revealed that these SGLT2i therapies lowered hospitalisations in HFpEF patients and even more so in patients with comorbid T2DM suggesting that they can be used to address acute decompensation. While they did not demonstrate the same degree of effect on all-cause mortality the drugs were useful in managing symptoms and reducing suffering. ARNIs showed only mild benefits in exercise performance and functional status and ambiguous results concerning survival prognosis.

Other interventional approaches that were effective included structured exercise regimes and other predominantly non-pharmacological interventions and organizational measures which contributed more toward the improvement of patients' objectively measured functional status and perceived quality of life. Both aerobic exercise and resistance training programs therefore enabled increased exercise capacity, decreased fatigue and dyspnoea levels and also meaningfully improved QOL as reported by patients. Nevertheless, sustaining participation in these programs still posed difficulties for participants especially those of the geriatric population with serious chronic illnesses. It was reported that changes in patients' behavioural patterns, such as reduction in salt intake and loss of weight have led to an improvement in symptoms and reduction in readmissions despite a problem of maintaining long-term compliance. The meta-analysis performed within this review also showed that, although pharmacological interventions are sufficient to prevent hospitalizations, non-pharmacological measures are more vital for enhancing the overall patient prognosis, indicating that the combination of these modalities is vital for the best HFpEF management.

These results are consistent with previous work highlighting the fact that the pathophysiology of HFpEF is very different from that of other types of HF, so it requires a more varied approach to the treatment. Pharmacological treatments especially SGLT2 inhibitors have recently gained evidential consideration in patients with HFpEF for successfully cutting hospitalization rates based on such trials as Pfeffer et al., (2019). Therefore, these globes suggest that SGLT2i not only ameliorates HFpEF symptoms but also improves concomitant metabolic comorbidities, such as diabetes, making them useful as foundation therapies in HFpEF. However, these clinical effects in terms of mortality did not achieve previous results suggesting that current pharmacological treatments for HFpEF are suboptimal as many patients in the condition have diastolic dysfunction, endothelial dysfunction and systemic inflammation.

The present non-pharmacological management also reinforces current data demonstrating that exercise and lifestyle changes are indispensable in treating HFpEF. The review performed by Passantino et al., (2021) also strengthened the role of exercise in enhancing functional capacity and functional limitation scores though the analysis of the present investigation is in overall confirmation of cardiac rehabilitation works in heart failure patients. However, setting up a controlled exercise regimen along with patient progression also varies, and the pragmatic nature of this study shows the importance of individualised approaches. The synthesis also indicates that even though lifestyle alterations can boost patient results, the longevity of the improvements is questionable, especially in communities with poor resource endowments.

The conclusions derived from this systematic review also concur with other systematic reviews, but they expand on them by incorporating the newest data regarding comparatively recently developed classes of pharmacological interventions such as SGLT2 inhibitors. Compared with the prior systematic reviews which were done before 2020 mainly based on the before-mentioned details on beta-blockers, ARBs and MRAs; few studies may have focused on the newer therapies like SGLT2i that are newly likely in the management of HFpEF (Mascolo et al., 2022). This review therefore validates our premise that whereas conventional pharmacotherapies such as beta blockers and MRAs are afforded a nominal level of efficacy in ameliorating symptoms they retain fair & poor efficacy against hospitalization procedures as well as mortality in HFpEF patients. They also mentioned that the studies included in this review revealed the impact of SGLT2i in terms of hospitalization and signs and symptoms which changed the treatment perspective.

Another way in which the current review departs from previous evaluations is this study puts relatively more weight on non-drug treatments including exercise programmes and diet changes. Earlier reviews included only pharmacological interventions while the literature contains much data

about significant positive effects of lifestyle interventions on the QoL and functional status. Using exercise and dietary intervention studies, the present review provides an integrated approach to the management of patients with HFpEF. However, the conclusions also show the inconsistency of the evidence sources, especially about the outcomes of lifestyle interventions, partially unnoticed by previous reviews. This warrants more extensive work to formulate definitive protocols in the management of HFpEF not through drug prescription but by implementing guideline-recommended nonpharmacological objectives (Upadhya & Kitzman, 2020).

4.2 Strengths and Limitations

As one of the major prominent features of this review, it implies the comprehensiveness of the approach and integrates pharmacological and non-pharmacologic therapies used in patients with HFpEF. The systematic approach followed the PRISMA guidelines thus minimizing a potential selection bias. The review included controlled trials, cohort studies, and systematic reviews, allowing for the combination of a wide area of evidence to maximize the generalizability of the study conclusions. The use of checklists such as the Cochrane Risk of Bias tool and the Newcastle-Ottawa Scale for quality assessment of the included studies also helped to confirm that all studies met methodological quality assessment (Kolaski et al., 2023).

Still, some limitations of the review can be noted that may put into question the results obtained during the work. Sources of studied participants, comparability of study designs, and the consistencies of interventional protocols seem to have introduced moderate levels of heterogeneity, especially in the body of nonpharmacologic trials. Also, even though the authors of the review focused only on the studies published during the last decade, it has been mentioned that only the articles published in English were included in the analysis; therefore, the authors could miss several essential data coming from other countries. Another weakness is that only published papers were included and the use of these made available on the Web of Science increases the probability of publication bias, as funnel plot analysis revealed that the distribution was asymmetrical (Afonso et al., 2024). This bias may lead to an overemphasized view of the effectiveness of particular interventional measures, particularly, exercise programs where studies with positive results are published most frequently, and large trials with negative results are likely to be omitted. In the future, more patients of different ages, genders and ethnicities should be involved and the protocols used to assess fall risk and incontinence should be even more uniform and less heterogeneous (Afonso et al., 2024).

4.3 Implications

The implications of the findings from this review to clinical practice are presented below regarding HFpEF patient care. Based on the evidence, the medications collectively categorized as SGLT2 inhibitors and ARNIs should be taken by those at the highest risk of hospitalization with diabetes and other metabolic disorders. Clinicians should also appreciate that available pharmacologies are currently ‘modest’ in enhancing LP survival (Lovelace et al., 2019) meaning that lifestyle interventions should not be neglected. It was recommended that exercise programs, cardiac rehabilitation, and dietary changes should be advised within a treatment plan to increase patient’s functional status, as well as their quality of life. However, since patients do not adhere to prescribed regimens well due to many factors, particularly in older adults, there is a need to use patient-centred approaches that consider patients’ characteristics and preferences (Lovelace et al., 2019).

From a policy perspective, the results also underscore the necessity for healthcare systems to fund community interventions that encourage change in individual behaviour, these include exercise classes and the use of a dietician. Other categories that need insurance reimbursement should also be widened to ease the cost on patients when paying for non-pharmacological treatments. Furthermore, current strategies should include the creation of clinical practice guidelines that enshrine both pharmacological and non-pharmacological approaches to enhance the handling of HFpEF (Sapna et al., 2023). Owing to the diverse nature of the disease presentation in HFpEF patients, it is improbable for the management of this condition to be generalised. Thus, the focus should be placed on the elaboration of person-static approaches to intervene in patients with HFpEF.

Several areas of future research were found in the course of this scholarly review as follows; One of the main research opportunities is the underpowered large randomized controlled trials to assess the effect of SGLT2 inhibitors and ARNIs on the mortality and quality of life in the vast patient population groups (Sagarra-Romero & Viñas-Barros, 2020). However, at this time, there is uncertainty about whether these therapies improve survival over the long term: Currently, these therapies appear to reduce hospitalization. However, there is a dearth of research on non-pharmacological treatments, especially concerning the longer-term effects of exercise and other exercise-based regimes. It would be important to use more exercise protocols and diet interventions uniformly across the studies to minimise heterogeneity and also to enhance the comparability of the evidence.

Future work should also aim to elucidate the mechanisms behind the development of HFpEF to find new treatable substrates. Because HFpEF has a non-stenoic pathophysiological process and reduced heart failure survival, management strategies that target diastolic dysfunction, endothelial function, and systemic inflammation may be superior to conventional pharmacological therapies. Furthermore, research should focus on how patients respond to lifestyle changes and different ways to increase their compliance in the identified vulnerable groups. Lastly, the inclusion of digital health technologies, including home monitoring to keep an eye on patient compliance and telehealth to deliver care and advice, might offer new strategies to enhance the management of HFpEF in actual world scenarios (Seixas et al., 2020).

5. Conclusion

The systematic review combined data from 22 studies focusing on the overview of a variety of pharmacological and non-pharmacological treatments of HFpEF. The main findings also assert the need for a comprehensive management strategy for HFpEF because it is such a heterogeneous condition. SGLT2i, and more specifically, ARNI were effective in decreasing the number of hospitalizations and controlling symptoms. Nonetheless, their effect on duration mortality is equivocal, which means that they control acute decompensation but fail to address the disease-modifying pathway of HFpEF. Whereas there were significant relative benefits with non-pharmacological interventions like structured exercise programs and other lifestyle changes in enhancing functional capacity and quality of life among the patients. Still, the benefits of this attending are paramount but due to high nonadherence to lifestyle changes reveals that there is a need to provide follow-up support to achieve long-term goals.

Thus, overall, despite the improvements in the management of HFpEF, some interesting and essential problems remain urgent that concern the increase in survival rates of HFpEF patients and their quality of life. Pharmacological treatment as well as diet and lifestyle interventions should be applied in parallel at present, although the need for larger and longer-term trials is apparent. The differences in patient responses also mean that there is a need for a health management approach that is patient specific, that is where the concept of personalized medicine is derived. The strategy for moving ahead will implicitly involve a multidisciplinary approach and tapping into expertise from clinicians, researchers, and policymakers to map out treatment trajectories and come up with even more creative strategies for dealing with both the stable and unstable conditions of HFpEF. With the relatively recent description of HFpEF, there is potential to alter the chronic disease management of patients with this diagnosis by utilizing integrated consumer-centred medical and other self-management interventions.

References

1. Abboud, A., & Januzzi, J. L. (2021). Reverse cardiac remodeling and ARNI therapy. Current heart failure reports, 18, 71-83.
2. Abdin, A., Böhm, M., Shahim, B., Karlström, P., Kulenthiran, S., Skouri, H., & Lund, L. H. (2024). Heart failure with preserved ejection fraction epidemiology, pathophysiology, diagnosis and treatment strategies. International Journal of Cardiology, 132304.
3. Afonso, J., Ramirez-Campillo, R., Clemente, F. M., Büttner, F. C., & Andrade, R. (2024). The perils of misinterpreting and misusing "publication Bias" in meta-analyses: an education review on funnel plot-based methods. Sports medicine, 54(2), 257-269.

4. Ali, H., Shahzil, M., Moond, V., Shahzad, M., Thandavaram, A., Sehar, A., ... & Tillmann, H. (2024). Non-Pharmacological Approach to Diet and Exercise in Metabolic-Associated Fatty Liver Disease: Bridging the Gap between Research and Clinical Practice. Journal of Personalized Medicine, 14(1), 61.
5. Batten, J., & Brackett, A. (2022). Ensuring rigor in systematic reviews: Part 6, reporting guidelines. Heart & Lung, 52, 22-25.
6. Bazoukis, G., Papadatos, S. S., Thomopoulos, C., Tse, G., Cheilidis, S., Tsioufis, K., & Farmakis, D. (2021). Impact of SGLT2 inhibitors on major clinical events and safety outcomes in heart failure patients: a meta-analysis of randomized clinical trials. Journal of Geriatric Cardiology: JGC, 18(10), 783.
7. Borlaug, B. A. (2020). Evaluation and management of heart failure with preserved ejection fraction. Nature Reviews Cardiology, 17(9), 559-573.
8. Candelaria, D., Randall, S., Ladak, L., & Gallagher, R. (2020). Health-related quality of life and exercise-based cardiac rehabilitation in contemporary acute coronary syndrome patients: a systematic review and meta-analysis. Quality of Life Research, 29(3), 579-592.
9. Casanova-Salas, I., Athie, A., Boutros, P. C., Del Re, M., Miyamoto, D. T., Pienta, K. J., ... & Mateo, J. (2021). Quantitative and qualitative analysis of blood-based liquid biopsies to inform clinical decision-making in prostate cancer. European urology, 79(6), 762-771.
10. Clinton, S. K., Giovannucci, E. L., & Hursting, S. D. (2020). The world cancer research fund/American institute for cancer research third expert report on diet, nutrition, physical activity, and cancer: impact and future directions. The Journal of nutrition, 150(4), 663-671.
11. Dankowski, R., Kotwica, T., Szyszka, A., Przewłocka-Kosmala, M., Sacharczuk, W., Karolko, B., ... & Kosmala, W. (2018). Determinants of the beneficial effect of mineralocorticoid receptor antagonism on exercise capacity in heart failure with reduced ejection fraction. Kardiologia Polska (Polish Heart Journal), 76(9), 1327-1335.
12. De Mello, R. G. B., Dalla Corte, R. R., Gioscia, J., & Moriguchi, E. H. (2019). Effects of physical exercise programs on sarcopenia management, dynapenia, and physical performance in the elderly: a systematic review of randomized clinical trials. Journal of aging research, 2019(1), 1959486.
13. Dykgraaf, S. H., Matenge, S., Desborough, J., Sturgiss, E., Dut, G., Roberts, L., ... & Kidd, M. (2021). Protecting nursing homes and long-term care facilities from COVID-19: a rapid review of international evidence. Journal of the American Medical Directors Association, 22(10), 1969-1988.
14. Franklin, B. A., Thompson, P. D., Al-Zaiti, S. S., Albert, C. M., Hivert, M. F., Levine, B. D., ... & American Heart Association Physical Activity Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; and Stroke Council. (2020). Exercise-related acute cardiovascular events and potential deleterious adaptations following long-term exercise training: placing the risks into perspective–an update: a scientific statement from the American Heart Association. Circulation, 141(13), e705-e736.
15. Graczyk, P., Dach, A., Dyrka, K., & Pawlik, A. (2024). Pathophysiology and Advances in the Therapy of Cardiomyopathy in Patients with Diabetes Mellitus. International Journal of Molecular Sciences, 25(9), 5027.
16. Hanada, M., Kasawara, K. T., Mathur, S., Rozenberg, D., Kozu, R., Hassan, S. A., & Reid, W. D. (2020). Aerobic and breathing exercises improve dyspnea, exercise capacity and quality of life in idiopathic pulmonary fibrosis patients: systematic review and meta-analysis. Journal of Thoracic Disease, 12(3), 1041.
17. John, L. K., Loewenstein, G., Marder, A., & Callaham, M. L. (2019). Effect of revealing authors' conflicts of interests in peer review: randomized controlled trial. bmj, 367.
18. Kalogirou, F., Forsyth, F., Kyriakou, M., Mantle, R., & Deaton, C. (2020). Heart failure disease management: a systematic review of effectiveness in heart failure with preserved ejection fraction. ESC heart failure, 7(1), 195-213.

19. Karunarathna, I., De Alvis, K., Gunasena, P., & Jayawardana, A. (2024). Designing and conducting clinical research: Methodological approaches.
20. Kelly, J. T., Campbell, K. L., Hoffmann, T., & Reidlinger, D. P. (2018). Patient experiences of dietary management in chronic kidney disease: a focus group study. Journal of Renal Nutrition, 28(6), 393-402.
21. Khan, S. (2023). Cardiac Rehabilitation: Benefits, Challenges, and Future Perspectives. Pakistan Journal of Medical & Cardiological Review, 1(01), 53-73.
22. Kolaski, K., Romeiser Logan, L., & Ioannidis, J. P. (2023). Guidance to best tools and practices for systematic reviews. Journal of Pediatric Rehabilitation Medicine, 16(2), 241-273.
23. Kris-Etherton, P. M., Petersen, K. S., Després, J. P., Anderson, C. A., Deedwania, P., Furie, K. L., ... & Ma, J. (2021). Strategies for promotion of a healthy lifestyle in clinical settings: pillars of ideal cardiovascular health: a science advisory from the American Heart Association. Circulation, 144(24), e495-e514.
24. Lefebvre, C., Glanville, J., Briscoe, S., Littlewood, A., Marshall, C., Metzendorf, M. I., ... & Cochrane Information Retrieval Methods Group. (2019). Searching for and selecting studies. Cochrane Handbook for systematic reviews of interventions, 67-107.
25. Liebgott, C., Chaib, I., Doyen, P., Robert, H., Eutamene, H., Duflos, G., ... & Mercier-Bonin, M. (2023). Fate and impact of nanoplastics in the human digestive environment after oral exposure: A common challenge for toxicology and chemistry. TrAC Trends in Analytical Chemistry, 117175.
26. Lovelace, D. L., McDaniel, L. R., & Golden, D. (2019). Long-term effects of breast cancer surgery, treatment, and survivor care. Journal of midwifery & women's health, 64(6), 713-724.
27. Ma, L. L., Wang, Y. Y., Yang, Z. H., Huang, D., Weng, H., & Zeng, X. T. (2020). Methodological quality (risk of bias) assessment tools for primary and secondary medical studies: what are they and which is better?. Military Medical Research, 7, 1-11.
28. Martinez, E. C., Valdés, J. R. F., Castillo, J. L., Castillo, J. V., Montecino, R. M. B., Jimenez, J. E. M., ... & Diarte, E. (2023). Ten steps to conduct a systematic review. Cureus, 15(12).
29. Mascolo, A., Di Mauro, G., Cappetta, D., De Angelis, A., Torella, D., Urbanek, K., ... & Rossi, F. (2022). Current and future therapeutic perspective in chronic heart failure. Pharmacological research, 175, 106035.
30. Minnella, E. M., Awasthi, R., Loiselle, S. E., Agnihotram, R. V., Ferri, L. E., & Carli, F. (2018). Effect of exercise and nutrition prehabilitation on functional capacity in esophagogastric cancer surgery: a randomized clinical trial. JAMA surgery, 153(12), 1081-1089.
31. Nair, N. (2020). Epidemiology and pathogenesis of heart failure with preserved ejection fraction. Reviews in cardiovascular medicine, 21(4), 531-540.
32. Nopp, S., Moik, F., Klok, F. A., Gattinger, D., Petrovic, M., Vonbank, K., ... & Zwick, R. H. (2022). Outpatient pulmonary rehabilitation in patients with long COVID improves exercise capacity, functional status, dyspnea, fatigue, and quality of life. Respiration, 101(6), 593-601.
33. O'Dea, R. E., Lagisz, M., Jennions, M. D., Koricheva, J., Noble, D. W., Parker, T. H., ... & Nakagawa, S. (2021). Preferred reporting items for systematic reviews and meta-analyses in ecology and evolutionary biology: a PRISMA extension. Biological Reviews, 96(5), 1695-1722.
34. Passantino, A., Dalla Vecchia, L. A., Corrà, U., Scalvini, S., Pistono, M., Bussotti, M., ... & La Rovere, M. T. (2021). The future of exercise-based cardiac rehabilitation for patients with heart failure. Frontiers in cardiovascular medicine, 8, 709898.
35. Peverill, M., Dirks, M. A., Narvaja, T., Herts, K. L., Comer, J. S., & McLaughlin, K. A. (2021). Socioeconomic status and child psychopathology in the United States: A meta-analysis of population-based studies. Clinical psychology review, 83, 101933.
36. Pfeffer, M. A., Shah, A. M., & Borlaug, B. A. (2019). Heart failure with preserved ejection fraction in perspective. Circulation research, 124(11), 1598-1617.
37. Prakash, A., Singh, H., Kaur, H., Semwal, A., Sarma, P., Bhattacharyya, A., ... & Medhi, B. (2020). Systematic review and meta-analysis of effectiveness and safety of favipiravir in the

management of novel coronavirus (COVID-19) patients. Indian Journal of Pharmacology, 52(5), 414-421.
38. Redfield, M. M., & Borlaug, B. A. (2023). Heart failure with preserved ejection fraction: a review. Jama, 329(10), 827-838.
39. Rodriguez-Mañas, L., Laosa, O., Vellas, B., Paolisso, G., Topinkova, E., Oliva-Moreno, J., ... & European MID-Frail Consortium. (2019). Effectiveness of a multimodal intervention in functionally impaired older people with type 2 diabetes mellitus. Journal of cachexia, sarcopenia and muscle, 10(4), 721-733.
40. Roger, V. L. (2021). Epidemiology of heart failure: a contemporary perspective. Circulation research, 128(10), 1421-1434.
41. Saez de Asteasu, M. L., Martínez-Velilla, N., Zambom-Ferraresi, F., Casas-Herrero, Á., Cadore, E. L., Ramirez-Velez, R., & Izquierdo, M. (2019). Inter-individual variability in response to exercise intervention or usual care in hospitalized older adults. Journal of cachexia, sarcopenia and muscle, 10(6), 1266-127
42. Sagarra-Romero, L., & Viñas-Barros, A. (2020). COVID-19: Short and long-term effects of hospitalization on muscular weakness in the elderly. International journal of environmental research and public health, 17(23), 8715.
43. Saldarriaga, C. L. A. R. A., Colin-Ramirez, E., Islam, S. U. N. J. I. D. A. T. U. L., Alemayehu, W. E. N. D. I. M. A. G. E. G. N., Macdonald, P. E. T. E. R., Ross, H. E. A. T. H. E. R., ... & Ezekowitz, J. A. (2024). Dietary Sodium Intake and Outcomes: a Secondary Analysis From Sodium-HF. Journal of cardiac failure, 30(9), 1073-1082.
44. Sanders, G. D., Maciejewski, M. L., & Basu, A. (2019). Overview of cost-effectiveness analysis. Jama, 321(14), 1400-1401.
45. Sapna, F. N. U., Raveena, F. N. U., Chandio, M., Bai, K., Sayyar, M., Varrassi, G., ... & Mohamad, T. (2023). Advancements in heart failure management: a comprehensive narrative review of emerging therapies. Cureus, 15(10).). Advancements in heart failure management: a comprehensive narrative review of emerging therapies. Cureus, 15(10).
46. Sarboozi Hosein Ábadi, T., Namazi Nia, M., & Mazlom, S. R. (2020). Effect of self-determination theory-based discharge program on lifestyle and readmission of patients with heart failure: A clinical trial. Evidence Based Care, 10(1), 25-35.
47. Seixas, A., Conners, C., Chung, A., Donley, T., & Jean-Louis, G. (2020). A pantheoretical framework to optimize adherence to healthy lifestyle behaviors and medication adherence: the use of personalized approaches to overcome barriers and optimize facilitators to achieve adherence. JMIR mHealth and uHealth, 8(6), e16429.
48. Svanström, H., Mkoma, G. F., Hviid, A., & Pasternak, B. (2024). SGLT-2 inhibitors and mortality among patients with heart failure with reduced ejection fraction: linked database study. bmj, 387.
49. Tabl, M. A., & Essawy, T. S. (2019). Effects of angiotensin receptor-neprilysin inhibitor on exercise capacity in patients with heart failure with reduced ejection fraction. Международный журнал сердца и сосудистых заболеваний, 7(24 (eng)), 15-19.
50. Tamaki, Y., Yaku, H., Morimoto, T., Inuzuka, Y., Ozasa, N., Yamamoto, E., ... & KCHF Study Investigators. (2021). Lower in-hospital mortality with beta-blocker use at admission in patients with acute decompensated heart failure. Journal of the American Heart Association, 10(13), e020012.
51. Tiwari, D., & Aw, T. C. (2024). Emerging Role of Natriuretic Peptides in Diabetes Care: A Brief Review of Pertinent Recent Literature. Diagnostics, 14(19), 2251.
52. Toth, P. P., & Gauthier, D. (2021). Heart failure with preserved ejection fraction: strategies for disease management and emerging therapeutic approaches. Postgraduate Medicine, 133(2), 125-139.
53. Tromp, J., Shen, L., Jhund, P. S., Anand, I. S., Carson, P. E., Desai, A. S., ... & McMurray, J. J. (2019). Age-related characteristics and outcomes of patients with heart failure with preserved ejection fraction. Journal of the American College of Cardiology, 74(5), 601-612.

54. Tsai, W. J., Wen, Y. K., Cheng, Y. Y., Huang, J. L., & Chen, Y. W. (2022). Effectiveness of home-based telerehabilitation programs on functional capacity and cardiac function in elderly heart failure patients: a prospective longitudinal study. Medicine, 101(28), e29799.
55. Tsutsui, H. (2022). Recent advances in the pharmacological therapy of chronic heart failure: evidence and guidelines. Pharmacology & Therapeutics, 238, 108185.
56. Upadhya, B., & Kitzman, D. W. (2020). Heart failure with preserved ejection fraction: new approaches to diagnosis and management. Clinical cardiology, 43(2), 145-155.
57. Vaduganathan, M., Claggett, B. L., Jhund, P. S., Cunningham, J. W., Ferreira, J. P., Zannad, F., ... & Solomon, S. D. (2020). Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials. The Lancet, 396(10244), 121-128.
58. Vitale, G., Romano, G., Di Franco, A., Caccamo, G., Nugara, C., Ajello, L., ... & Sarullo, F. M. (2019). Early effects of sacubitril/valsartan on exercise tolerance in patients with heart failure with reduced ejection fraction. Journal of clinical medicine, 8(2), 262.
59. Wylie, L. J., Park, J. W., Vanhatalo, A., Kadach, S., Black, M. I., Stoyanov, Z., ... & Piknova, B. (2019). Human skeletal muscle nitrate store: influence of dietary nitrate supplementation and exercise. The Journal of physiology, 597(23), 5565-5576.
60. Yaku, H., Kato, T., Morimoto, T., Inuzuka, Y., Tamaki, Y., Ozasa, N., ... & KCHF Study Investigators. (2019). Association of mineralocorticoid receptor antagonist use with all-cause mortality and hospital readmission in older adults with acute decompensated heart failure. JAMA network open, 2(6), e195892-e195892.
61. Yang, D., Zhang, Y., Yan, J., Liu, M., & An, F. (2022). SGLT-2 inhibitors on prognosis and health-related quality of life in patients with heart failure and preserved ejection fraction: A systematic review and meta-analysis. Frontiers in Cardiovascular Medicine, 9, 942125.