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Effectiveness of Angiotensin Converting Enzyme Inhibitors and Beta-Blockers in Reducing Mortality in Patients with Congestive Heart Failure

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Abstract

CHF is a chronic and progressive cardiovascular disease with high morbidity, frequent hospitalization and a high mortality rate, especially for individuals with HFREF. The purpose of this study is to assess the efficacy of angiotensin converting enzyme inhibitors and beta blockers in the reduction of mortality in congestive heart failure patients especially in terms of the neurohormonal modulation and long-term clinical results. In this study, a narrative literature review design was used to obtain secondary data from national and international journals, textbooks, ClinicalKey, ScienceDirect, PubMed, Google Scholar, scientific websites of publishers, and other relevant scientific sources. The existing literature focused on studies from 2015 to 2026, with the exception of landmark studies from the past that provided foundational evidence relevant to heart failure pharmacotherapy. The results suggest that ACE inhibitors and beta blockers are associated with consistently lower mortality, hospitalization rate and clinical stability, particularly in those with heart failure with reduced EF. Angiotensin converting enzyme inhibitors (ACE inhibitors) can help decrease the harmful effects of activation of the renin angiotensin aldosterone system (RAAS) while beta blockers can help to reduce excessive sympathetic nervous system activity. They both have complementary neurohormonal control and can have a wider clinical effect than monotherapy, if used appropriately. The therapeutic efficacy, however, is not consistent in every patient, and may be affected by the level of ejection fraction (EF), age, comorbidities, disease severity, drug tolerance, dose optimization, and adherence to therapy. This review demonstrates that ACE inhibitors and beta blockers are still employed by patients with CHF and are still considered critical components of guideline directed pharmacologic therapy, especially in those patients with reduced EF.

Introduction

Congestive Heart Failure (CHF) is a chronic and progressive clinical condition characterized by the heart's inability to pump blood adequately to meet the body's metabolic needs (Pugliatti et al., 2024). This disease is one of the leading causes of morbidity and mortality worldwide, particularly among the elderly population (Zhou et al., 2026; Gianfredi et al., 2025; Safiri et al., 2023). Along with the rising prevalence of cardiovascular disease, the burden of CHF continues to increase both clinically and economically. This condition is often accompanied by various comorbidities such as hypertension, diabetes mellitus, and coronary artery disease, which worsen patient prognosis. Therefore, a comprehensive, evidence-based therapeutic approach is needed to reduce mortality rates and improve the quality of life for patients with CHF (Tran et al., 2025; Yang et al., 2024; Suleman et al., 2026).

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Although significant advances in treatment have been made, long-term mortality among CHF patients remains high, particularly among those with heart failure with reduced ejection fraction (HFrEF) (Parizad et al., 2026; Biegus et al., 2026; Lund et al., 2026). In this condition, the left ventricular ejection fraction decreases, significantly impairing the heart's pumping function. This triggers the activation of neurohormonal- e compensatory mechanisms, such as the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system, which are initially adaptive but, in the long term, actually worsen the heart's condition. Sustained activation of these systems leads to ventricular remodeling, fluid retention, and increased blood pressure, all of which contribute to increased mortality (Tang et al., 2025; Mocan et al., 2025; Gaydarski et al., 2025).

In modern clinical practice, guideline-directed medical therapy (GDMT) has become the primary approach in the management of CHF (Shahverdi et al., 2026; Patolia et al., 2023; Fetene et al., 2026). This therapy focuses on modulating neurohormonal systems through the use of medications such as beta-blockers and angiotensin-converting enzyme inhibitors (ACE inhibitors). Both classes of drugs have been shown to reduce mortality rates and the incidence of readmissions in CHF patients. The use of guideline-based therapy also aims to slow disease progression and improve overall cardiac function. Thus, the implementation of GDMT has become the gold standard in CHF management across various healthcare facilities (Hassan et al., 2024).

Beta-blockers are a key component of CHF therapy that work by inhibiting the activity of the sympathetic nervous system (Mancia et al., 2022; Nasoufidou et al., 2025; Milhem et al., 2025). These medications reduce heart rate, decrease myocardial oxygen demand, and prevent fatal arrhythmias that can lead to sudden death. Additionally, beta-blockers play a role in improving left ventricular function and inhibiting cardiac remodeling. Several types of beta-blockers, such as bisoprolol and carvedilol, have been extensively studied and have shown consistent results in reducing mortality in CHF patients. This effectiveness makes beta-blockers a first-line therapy in the management of chronic heart failure (Groote et al., 2007).

On the other hand, ACE inhibitors work by inhibiting the conversion of angiotensin I to angiotensin II, thereby reducing vasoconstriction and aldosterone secretion (Miura et al., 2025; Ahmad et al., 2023; Gomera et al., 2026). These effects lead to a decrease in blood pressure, reduced fluid retention, and a reduction in the heart's workload. Additionally, ACE inhibitors also have a protective effect against ventricular remodeling, a key factor in the progression of CHF. Drugs such as enalapril and lisinopril have been proven effective in reducing cardiovascular mortality and improving patient survival. Therefore, ACE inhibitors are one of the recommended first-line therapies in the management of CHF (Hassan et al., 2024).

The combination of beta-blockers and ACE inhibitors provides a synergistic effect in suppressing excessive neurohormonal activation. With complementary mechanisms of action, these two drugs are able to provide optimal protection for heart function. Studies show that the use of this combination therapy can reduce hospitalization rates and improve survival rates in CHF patients compared to monotherapy. These additional benefits highlight the importance of a combination therapy approach in achieving better clinical outcomes (Tang et al., 2025).

Strong clinical evidence regarding the effectiveness of beta-blockers can be seen in the results of the Cardiac Insufficiency Bisoprolol Study II (CIBIS-II) (Castiello et al., 2026; Beavers & Carter, 2026; Alsagaff et al., 2026). This study demonstrated that bisoprolol significantly reduced overall mortality by approximately 32% compared to placebo in patients with stable CHF. Additionally, there was a reduction in sudden death and hospitalizations due to heart failure. These results reinforce the role of beta-blockers as a primary therapy in reducing the risk of death in CHF patients, regardless of the disease's etiology or the severity of left ventricular dysfunction (Groote et al., 2007; Böhm et al., 2026).

Other studies also indicate that the benefits of beta-blockers are not limited to patients with HFrEF but also extend to those with mildly reduced or preserved ejection fractions. This suggests that beta-blocker use offers broad benefits across the spectrum of heart failure. Furthermore, this therapy has been shown to positively impact patients' quality of life and reduce the incidence of readmissions. These findings further reinforce the importance of beta-blocker use in daily clinical practice (Matsumoto et al., 2025).

Nevertheless, several challenges remain in the implementation of combination therapy with beta-blockers and ACE inhibitors, particularly regarding initiation strategies and dose optimization. Several studies indicate that the sequence of drug administration may influence clinical outcomes, although the differences are not always significant. Furthermore, patient characteristics such as age, comorbidities, and drug tolerance are also critical considerations in determining the appropriate therapy. This underscores that a personalized therapeutic approach remains essential in the management of CHF (Geavlete & Chioncel, 2024).

Based on the above discussion, it can be concluded that beta-blocker and ACE inhibitor therapy plays a crucial role in reducing mortality in patients with CHF. However, there remains a research gap regarding long-term efficacy, optimal combination strategies, and therapeutic response in specific subpopulations. Therefore, further research is urgently needed to evaluate the efficacy of these therapies more comprehensively. The research findings are expected to contribute to the advancement of scientific knowledge and serve as a basis for more effective and targeted clinical decision-making (Rahayu et al., 2025).

The objective of this study is to analyze and determine the efficacy of ACE inhibitor and beta-blocker therapy in reducing mortality in patients with Congestive Heart Failure (CHF), particularly in patients with heart failure with reduced ejection fraction (HFrEF), as well as to evaluate the role of the combination therapy of these two medications in improving clinical outcomes, including reduced mortality and hospitalization rates. Additionally, this study aims to identify the effects of the mechanisms of action of both therapies on the neurohormonal system and assess their potential long-term benefits across various patient characteristics in CHF, thereby providing a scientific basis for optimizing more effective and evidence-based therapeutic strategies.

Methods

Research Design

The study used a method of literature review, in which the literature was reviewed in the form of a narrative review design to discuss the efficacy of angiotensin converting enzyme inhibitors and beta blockers in reducing mortality in patients with congestive heart failure. The design was chosen since the study was not designed to quantify pooled statistical effects or perform a meta analysis, but rather designed to synthesize and critically analyze existing evidence. The inclusion of the above-mentioned types of studies in the review was facilitated by this.This enabled the review to incorporate the results of various study types such as narrative reviews, systematic reviews, meta analysis, observational studies, clinical outcome studies, and relevant scientific reports.

The narrative review design was also suitable as they could not only be understood in terms of mortality outcomes. These therapies have strong links with neurohormonal activation, ventricular remodeling, hospitalization risk, cardiac function, ejection fraction category, comorbidities and adherence. Hence, this review was aimed to elucidate not only whether these therapies lower mortality but also how the clinical effects are mediated and why the benefits of these therapies may be different in patients with different heart failure phenotypes.

Literature Sources and Search Strategy

The literature survey was carried out in February 2026, with secondary data collected from scientific journals and other literature sources around the globe. The sources were PubMed, Google Scholar, ClinicalKey, Science Direct, journal publishers' websites, textbooks and scientific publications. The sources were chosen to represent peer-reviewed articles and scientific materials regarding cardiovascular pharmacotherapy and care of CHF.

Literature was searched for on the topics of congestive heart failure, heart failure with reduced ejection fraction, angiotensin converting enzyme inhibitors, beta blockers, mortality, hospitalization, neurohormonal activation, RAAS inhibition, sympathetic nervous system inhibition, ventricular remodeling, and guideline directed medical therapy. These terms used were: “congestive heart failure,” “heart failure with reduced ejection fraction,” “ACE inhibitors,” “angiotensin converting enzyme inhibitors,” “beta blockers,” “mortality,” “hospitalization,” “neurohormonal activation,” “RAAS inhibition,” and “sympathetic nervous system inhibition.” The keywords were used both individually and in combination to locate relevant literature for the aim of the study.

Inclusion dan Exclusion Criteria

Scientific publications and academic sources including the discussion of ACE inhibitors, beta-blockers or general pharmacotherapy in cases of Congestive heart failure were included. Inclusion of studies in patients with heart failure with reduced ejection fraction (HFrEF) was prioritized due to a strong clinical association with neurohormonal activation and mortality benefit with pharmaceuticals. Articles were accepted if they reported on at least one aspect of an outcome that was considered relevant (all cause mortality, cardiovascular mortality, hospitalization, ventricular remodeling, cardiac function, quality of life, therapeutic response, variation of outcome by EF category, and comorbidity).

Literature published within the timeframe 2015–2026 was considered and given priority, reflecting recent advances in heart failure therapy. In older landmark studies, however, the studies were included when they offered fundamental evidence that was still relevant to the role of ACE inhibitors or beta blockers in chronic heart failure. This was required because a few of the earlier studies continue to be influential in the established therapeutic basis of heart failure management.

Articles that did not relate to congestive heart failure, heart failure pharmacotherapy, ACE inhibitors, beta blockers, mortality, hospitalization or relevant clinical outcomes were excluded. Sources that contained only non-pharmacological interventions were not used as primary sources. Articles that did not provide clarity on scientific validity, incomplete information on methodology, and were not fully accessible (no full text) were also eliminated.

Literature Selection Process

The process of selecting was done in a phased manner. The chosen scientific sources and predetermined keywords were used to identify articles in the first step. The titles and abstracts were then scanned to identify those that were relevant to the study topic. If articles were found relevant, they were considered in greater detail by looking at the full text or information available from science literature associated with the article's goals, methodology, results and conclusions.

Selected studies were then categorized based on the major themes of the review following the screening. Central evidence consisted of studies that explicitly mentioned a reduction in mortality. Some studies were included that discussed beta blockers in mildly reduced or preserved EF, comorbidities or characteristics of patient to explain variation in therapeutic response. Both of these steps ensured that the review kept to ACE inhibitors and beta blockers, and recognized the heterogeneity of heart failure patients.

Data will be extracted and analyzed.

The information was gathered by identifying the author, year of publication, article title, study design, major findings and conclusions of the chosen sources. The information obtained was then put into a literature review table in order to have a clear overview of the studies included in the literature review. This table was used to facilitate the narrative synthesis and to illustrate the contribution of each study in the discussion of ACE inhibitor and beta blocker therapy in CHF.

A thematic narrative analysis was used to analyze the selected literature. The analysis was broken down into five broad themes: role of neurohormonal activation in CHF mortality, effect of ACE inhibitors, efficacy of beta blockers, and synergy of combination therapy, and the effect of ejection fraction and clinical variables. Because this study was a narrative review design, no pooled effect size, risk ratio and odd ratio were calculated, nor was a meta analytic calculation performed. The results were qualitatively analyzed by taking into account the study design, its relevance to the research goal, the characteristics of the population studied, the clinical outcomes, and the consistency of the results with the literature reviewed

Result and Discussion

Table 1. Characteristics of Studies Included in the Literature Review on ACE Inhibitor and Beta Blocker Therapy in Congestive Heart Failure

No	Author	Title	Method	Main Findings	Conclusion
1	Arnold et al. (2023)	Beta Blocker Use and Heart Failure Outcomes in Mildly Reduced and Preserved Ejection Fraction	Observational cohort study	Beta blocker use was associated with clinical outcomes in patients with mildly reduced and preserved ejection fraction, with stronger relevance in mildly reduced ejection fraction.	Beta blockers may be useful in selected heart failure patients beyond HFrEF, but the benefit depends on ejection fraction and patient characteristics.
2	Bavishi et al. (2015)	Beta Blockers in Heart Failure with Preserved Ejection Fraction: A Meta Analysis	Meta analysis	Beta blockers showed possible mortality benefit in HFpEF, although the evidence was less consistent than in HFrEF.	Beta blockers may have potential benefit in HFpEF, but the evidence remains weaker than in reduced ejection fraction heart failure.
3	Beer et al. (2025)	Beta Blockers in Patients with Heart Failure with Reduced Ejection Fraction and Concomitant Chronic Obstructive Pulmonary Disease: Cardiovascular and Respiratory Outcomes	Observational study	Cardioselective beta blockers were associated with favorable cardiovascular outcomes in HFrEF patients with COPD without clear evidence of major respiratory harm.	Beta blockers can be considered in HFrEF patients with COPD when clinically appropriate and carefully monitored.
4	Burnett et al. (2017)	Thirty Years of Evidence on the	Network meta analysis	Drug therapies targeting	Neurohormonal modulation is

		Efficacy of Drug Treatments for Chronic Heart Failure With Reduced Ejection Fraction: A Network Meta Analysis		neurohormonal pathways, including ACE inhibitors and beta blockers, reduced all cause mortality in HFrEF patients.	central in improving survival among patients with HFrEF.
5	Geavlete and Chioncel (2024)	Prognostic Impact of Heart Failure Pharmacotherapies in Acute Heart Failure: Strong Association in Mildly Reduced Ejection Fraction	Editorial or commentary	Heart failure pharmacotherapies showed prognostic relevance, especially in mildly reduced ejection fraction.	Treatment response in heart failure should be interpreted according to clinical phenotype and ejection fraction category.
6	Groote et al. (2007)	Bisoprolol in the Treatment of Chronic Heart Failure	Narrative review	Bisoprolol reduced mortality, sudden death, and hospitalization in chronic heart failure and improved clinical stability.	Bisoprolol supports the role of beta blockers as important therapy in chronic heart failure.
7	Hassan et al. (2024)	Comparative Efficacy and Long Term Outcomes of Beta Blockers Alone or in Combination With Angiotensin Converting Enzyme Inhibitors in Chronic Heart Failure: A Systematic Review	Systematic review	The article reported that beta blockers and ACE inhibitors reduce mortality and hospitalization, especially when used in combination.	The article concluded that combination therapy may provide better outcomes than monotherapy.
8	Matsumoto et al. (2025)	Beta Blocker Use and Outcomes in Patients with Heart Failure and Mildly Reduced and Preserved Ejection Fraction	Clinical outcome study	Beta blocker benefit was clearer in patients with mildly reduced ejection fraction, while findings in preserved ejection fraction were less consistent.	Beta blockers may benefit selected HFmrEF patients, but the evidence in HFpEF remains uncertain.
9	Rahayu et al. (2025)	Hubungan Profil Pasien Gagal Jantung terhadap Efektivitas Terapi Kombinasi Antihipertensi di Rawat Inap RSUD dr. Loekmono Hadi Kudus	Observational study	Patient profile, comorbidities, and clinical characteristics influenced the effectiveness of combination antihypertensive therapy in hospitalized heart failure patients.	Individual patient characteristics should be considered when evaluating the effectiveness of combination therapy.

10	Tang et al. (2025)	Pharmacotherapy in Patients with Heart Failure with Reduced Ejection Fraction: A Systematic Review and Meta Analysis	Systematic review and meta analysis	Pharmacological therapy for HFrEF, including ACE inhibitors and beta blockers, reduced mortality and hospitalization risk.	ACE inhibitors and beta blockers remain essential therapies for improving survival in HFrEF patients.

The Role of Neurohormonal Activation in Congestive Heart Failure Mortality

Chronic activation of the renin angiotensin aldosterone system and the sympathetic nervous system play a close role in the progression of congestive heart failure. These mechanisms can help to maintain blood pressure and tissue perfusion in the early stage of cardiac dysfunction. When activation is chronic, however, the same mechanisms are dysregulated, and involve the course of disease. Too much activation of the RAAS system leads to increased activity of angiotensin II and aldosterone, which in turn leads to vasoconstriction and retention of sodium ions, fluid, myocardial fibrosis, and increased myocardial workload. Simultaneously, chronic sympathetic hyperactivity raises the risk of arrhythmias, myocardial oxygen demand, long term cardiac stress, and heart rate.

The mechanisms account for the increased interest in modulating neurohormones as a major treatment strategy in heart failure. The progressive biological impact of unchecked neurohormonal activation is also a driver of mortality in CHF, especially in HFrEF, in addition to reduced cardiac pumping capacity. This view is confirmed by the finding of Burnett et al. (2017) that therapies aimed at neurohormonal pathways improve survival in patients with chronic heart failure with reduced ejection fraction. This evidence further reinforces the role of ACE inhibitors and beta blockers in their ability to directly modify the pathways that lead to cardiac worsening, recurrent decompensation and cardiovascular mortality.

Thus, effectiveness of ACE inhibitors and beta blockers should be considered in terms of their effect on the pathological process of CHF. ACE inhibitors inhibit the detrimental actions of excess RAAS activity and beta blockers slow down the excess sympathetic activity. If these therapies are used properly, they can alleviate cardiac work, limit ventricular remodeling, limit arrhythmia risk and enhance long term clinical results. This mechanism is especially important in HFrEF where neurohormonal activation is a major contributor to the disease process and death.

The Effectiveness of ACE Inhibitors in Reducing Mortality

One of the cornerstones of congestive heart failure (CHF) treatment is the use of ACE inhibitors, particularly those with poor ejection fractions. They primarily act by blocking the angiotensin converting enzyme (ACE), which prevents the conversion of angiotensin I into angiotensin II. With the decreased angiotensin II activity, the activity of vasoconstriction, aldosterone, sodium retention, and fluid overload all decrease. All these effects are clinically relevant as they reduce the workload to the failing heart and increase hemodynamic stability.

The literature reviewed confirms that ACE inhibitors can be considered as disease modifying drugs and not just symptom relieving drugs. Tang et al. (2025) demonstrates that pharmacotherapy, including ACE inhibitor based therapy, in HFrEF, is associated with reductions in the risk of all-cause mortality, cardiovascular mortality and hospitalization. This is in line with the goal of the present review as it is directly linked to the objective of improving survival in HF-RF patients with ACE inhibitor treatment. One of the advantages of ACE inhibitors is that it slows or prevents remodeling of the ventricles, which is one of the most important factors contributing to long term prognosis in CHF.

However, the results of ACE inhibitors' effectiveness should be interpreted only for the population discussed. Outcomes in heart failure with reduced EF may be more variable in other heart failure phenotypes, and are best evidenced in patients with HFrEF. However, in the clinical practice, factors like dose titration, renal function, blood pressure, potassium levels, comorbidities and patient compliance also play a role in the effectiveness of ACE inhibitors. This indicates that ACE inhibitors may offer tremendous survival benefit, which needs monitoring and fine-tuning by the individual patient.

The Effectiveness of Beta Blockers in Reducing Mortality and Sudden Death

Beta blockers are also an important component of heart failure therapy, due to their anti-sympathetic properties. Excessive sympathetic stimulation in patients with CHF raises the risk for fatal arrhythmias, HR, myocardial oxygen use and ventricular irritability. Beta blockers inhibit the beta adrenergic receptors which helps to reduce the stress on the heart, improves ventricular filling time, stabilizes cardiac rhythm and aids in reverse remodeling on long-term use.

The data presented in this article reveal the importance of beta blockers in patients with HFrEF. Groote et al. (2007) examines the potential of bisoprolol in chronic heart failure and reveals that this therapy results in better clinical stability, reduces the risk of hospitalization and lowers mortality. This confirms the protective role of beta blockers in sudden cardiac death and suggests a beneficial role in heart failure overall. They have beneficial effects on the long term use of left ventricular function and the development of cardiac remodeling.

The discussion of the efficacy of beta blockers should be approached with caution, however, as not all of the studies in the review are based on HFrEF. For heart failure with preserved ejection fraction, for instance, Bavishi et al. (2015) target beta blockers. Hence, this source should NOT be the primary source of evidence for mortality reduction in HFrEF. It is more suitable to apply this to illustrate that the effects of beta blockers in HFpEF have not been as consistent and should be interpreted with caution. Likewise, both Arnold et al. (2023) and Matsumoto et al. (2025) are helpful to remind the reader that the results of beta blockers could be different for patients with HFpEF versus those with HFmrEF. This distinction is relevant to keep the discussion focused on the central theme of this article, which is reducing mortality in CHF, especially those with reduced EF.

Synergistic Effects of the Combination of ACE Inhibitors and Beta Blockers

The rationale for combining the two drugs is based on the fact that both ACE inhibitors and beta blockers have different, but related mechanisms of action, in the progression of CHF. These medications primarily inhibit the activation of RAAS and excess sympathetic nervous system activity, respectively. Combined therapy is a more comprehensive approach to neurohormonal control than either pathway alone because both are involved in ventricular remodeling, fluid overload, arrhythmia, and decreasing the cardiac function.

The evidence reviewed here suggests that the notion of combined neurohormonal blockade is of high relevance in the management of HFrEF. Burnett et al. (2017) demonstrates that drug therapies that focus on neurohormonal pathways have a beneficial effect on survival in chronic HFrEF, while Tang et al. (2025) confirms the beneficial effect of pharmacotherapy on reducing the risk of death and hospital admissions in HFrEF patients. Based on these results, it is not too farfetched to suggest that the use of ACE inhibitors and beta blockers could be considered a complementary approach in the treatment of CHF. The article should not make the claim that each of the studies included in the review definitely demonstrates the superiority of combination therapy, however, since several studies reviewed in this article represent only beta blockers, or larger populations of patients with heart failure, the article should not identify combination therapy as a universal solution.

The mechanisms of these therapies are best explained for the synergistic effect. ACE inhibitors work by inhibiting the RAAS, which prevents vasoconstriction, fluid retention and structural remodeling. Beta blockers have been shown to decrease the risk of arrhythmia, heart rate, sympathetic stress, and myocardial oxygen demand. With appropriate use, both can act on the biological mechanisms of disease progression from hemodynamic and neurohormonal sides in a derogatory way. This gives a more solid therapeutic platform to enhance survival, decrease hospitalization, and maintain cardiac function in HFrEF patients.

It is important to gradually increase the doses of combination therapy and monitor patients during clinical use. Hypotension, renal function, bradycardia, electrolyte disturbances, comorbidities and drug tolerance need to be taken into account. Thus, not only the pharmacological characteristics of the drugs, but also the individualization and long-term maintenance of the therapy, are important for the effectiveness of combination therapy.

The Influence of Ejection Fraction and Clinical Factors on Outcomes

Ejection fraction category has a strong influence on the efficacy of ACE inhibitors and beta blockers. Patients with HFrEF tend to benefit the most, as the pathophysiological mechanisms of HFrEF are linked to systolic dysfunction, ventricular remodeling and activation of neurohormonal systems. That is why there is the most evidence for ACE inhibitors and beta blockers in this group. Patients with HFpEF may also have more complex mechanisms, such as increasing myocardial stiffness with ageing, hypertension, metabolic disorders, obesity, atrial fibrillation and multiple co-morbidities. This means that treatment effects in HFpEF are less predictable.

This variation can be explained by several studies in the literature reviewed. There is some indication that the benefit of beta blocker is more pronounced in those with a mildly reduced ejection fraction, compared to those with preserved ejection fraction, according to Arnold et al. (2023) and Matsumoto et al. (2025). Bavishi et al. (2015) also shows that the evidence for beta blockers in HFpEF is not as strong as the evidence in HFrEF. These findings have importance because they help to avoid too sweeping of claims in the article. However, the benefits of beta blockers cannot be applied uniformly to all the heart failure phenotypes, taking into account the patient's ejection fraction category.

Treatment results are also affected by comorbidities. When carefully selected and monitored, beta blockers can still be beneficial to the heart and blood vessels for patients with HFrEF with comorbid chronic obstructive pulmonary disease (COPD), as demonstrated by Beer et al. (2025). This discovery is clinically significant since the majority of CHF patients have a variety of co-morbidities that make treatment decisions difficult. The patient profile and clinical characteristics also have an impact on the effectiveness of combination therapy in heart failure care, which is consistent with Rahayu et al. (2025). While local data should be viewed with caution, it does tell us something about the potential for therapeutic success in the real world, which is influenced by the patient, adherence, and clinical context.

From the literature reviewed, ACE inhibitors and beta blockers continue to be vital medicines in the management of CHF, particularly in HFrEF. They are most recognisable in terms of mortality reduction, prevention of hospitalisation, inhibition of ventricular remodeling and improvement of long term clinical outcomes. But these benefits do not apply to all patients. Therapeutic success is influenced by various factors: ejection fraction, disease severity, comorbidities, drug tolerance, dose optimization and adherence. Thus, the results of this review confirm the efficacy of guideline-directed pharmacological treatment and reinforce the need to tailor the treatment to the individual patient with CHF.

Conclusion

ACE inhibitor and beta-blocker therapy are the mainstays of treatment for congestive heart failure (CHF), particularly in heart failure with reduced ejection fraction (HFrEF), as they work synergistically to inhibit the activation of the neurohormonal system. ACE inhibitors suppress the renin-angiotensin-aldosterone system (RAAS), thereby reducing vasoconstriction, fluid retention, and ventricular remodeling, while beta-blockers inhibit the sympathetic nervous system, which plays a role in arrhythmias and sudden death. Various studies indicate that these two therapies, particularly when used in combination, can reduce mortality, decrease hospitalizations, and improve cardiac function and patients' quality of life. Their effectiveness is most consistent in patients with reduced ejection fraction, but remains influenced by clinical factors such as age, disease severity, comorbidities, adherence, and dose optimization; therefore, their application must be tailored according to the principles of guideline-directed medical therapy (GDMT).

Based on this, further research with a prospective design and a broader population is needed to evaluate long-term effectiveness and optimal therapeutic strategies. In clinical practice, it is important to optimize the implementation of GDMT through healthcare professional education, continuous therapy monitoring, and a multidisciplinary approach. Additionally, enhancing patient education regarding medication adherence, a healthy lifestyle, and early detection of decompensation is essential to reduce rehospitalization rates and improve the quality of life for CHF patients.

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References

Ahmad, H., Khan, H., Haque, S., Ahmad, S., Srivastava, N., & Khan, A. (2023). Angiotensin-converting enzyme and hypertension: a systemic analysis of various ACE inhibitors, their side effects, and bioactive peptides as a putative therapy for hypertension. Journal of the Renin-Angiotensin-Aldosterone System, 2023, 7890188. https://doi.org/10.1155/2023/7890188

Alsagaff, M. Y., Afrilla, D., Jannati, D., Nilamsari, W. P., Maghfirah, I., & Jaya, H. P. (2026). Poorer Clinical Outcomes and Longer Hospitalization with Beta Blocker Discontinuation in Acute Decompensated Heart Failure Wet and Warm: A Retrospective Study. Hospital Pharmacy, 00185787251410044. https://doi.org/10.1177/00185787251410044

Arnold, S. V., Silverman, D. N., Gosch, K., Nassif, M. E., Infeld, M., Litwin, S., Meyer, M., & Fendler, T. J. (2023). Beta-Blocker Use and Heart Failure Outcomes in Mildly Reduced and Preserved Ejection Fraction. JACC: Heart Failure, 11(8), 893–900. https://doi.org/10.1016/j.jchf.2023.03.017

Bavishi, C., Chatterjee, S., Ather, S., Patel, D., & Messerli, F. H. (2015). Beta-Blockers in Heart Failure with Preserved Ejection Fraction: A Meta-Analysis. Heart Failure Reviews, 20(2), 193–201. https://doi.org/10.1007/s10741-014-9453-8

Beavers, J., & Carter, S. (2026). Revisiting Beta-Blocker Formulation—What's Old Is New Again. Journal of Cardiac Failure-Intersections, 2(1), 27-29.

Beer, B. N., Benson, L., Basile, C., Schrage, B., Becher, P. M., Blankenberg, S., Kirchhof, P., Szabó-Söderberg, B., Metra, M., Lindberg, A., Imbalzano, E., Rosano, G. M. C., Karlström, P., Mol, P. G. M., Scorza, R., Lund, L. H., Lindberg, F., & Savarese, G.

(2025). Beta-Blockers in Patients with Heart Failure with Reduced Ejection Fraction and Concomitant Chronic Obstructive Pulmonary Disease: Cardiovascular and Respiratory Outcomes. European Journal of Heart Failure, 27(12), 2858–2868. https://doi.org/10.1002/ejhf.70046

Biegus, J., Bayes-Genis, A., von Haehling, S., Kosmala, W., Markwirth, P., Papp, Z., ... & Böhm, M. (2026). Contemporary Heart Failure Evidence in 2025: A Joint Summary of Key Trials from the European Journal of Heart Failure and ESC Heart Failure Journal. European Journal of Heart Failure, xuag015. https://doi.org/10.1093/ejhf/xuag015

Böhm, M., Abdullakutty, J., Bauersachs, J., Bavendiek, U., Bayes-Genis, A., Bhattacharyya, K., ... & Zannad, F. (2026). European Journal of Heart Failure International Expert Position Paper Utilisation, Optimisation, and Clinical Benefits of Steroidal Mineralocorticoid Receptor Antagonists in Heart Failure with a Reduced Ejection Fraction. European Journal of Heart Failure, xuag106. https://doi.org/10.1093/ejhf/xuag106

Burnett, H., Earley, A., Voors, A. A., Senni, M., McMurray, J. J. V., Deschaseaux, C., & Cope, S. (2017). Thirty Years of Evidence on the Efficacy of Drug Treatments for Chronic Heart Failure With Reduced Ejection Fraction. Circulation: Heart Failure, 10(1). https://doi.org/10.1161/CIRCHEARTFAILURE.116.003529

Castiello, D. S., Calvelli, P., Anniballo, A., Romano, L. R., Polimeni, A., & Curcio, A. (2026). The prognostic impact of beta blockers in ischemic heart failure: time for a paradigm shift?. Heart Failure Reviews, 31(1), 41. https://doi.org/10.1007/s10741-026-10615-5

Fetene, A., Degu, A., Kassaw, C., Fekadu Oljira, C., Gubae, K., Shimels, T., & Alemkere, G. (2026). Evaluating the implementation of guideline-directed medical therapy in the treatment of chronic heart failure at public hospitals in Ethiopia. Therapeutic Advances in Cardiovascular Disease, 20, 17539447251411121. https://doi.org/10.1177/17539447251411121

Gaydarski, L., Petrova, K., Stanchev, S., Pelinkov, D., Iliev, A., Dimitrova, I. N., ... & Stamenov, N. (2025). Morphometric and molecular interplay in hypertension-induced cardiac remodeling with an emphasis on the potential therapeutic implications. International Journal of Molecular Sciences, 26(9), 4022. https://doi.org/10.3390/ijms26094022

Geavlete, O., & Chioncel, O. (2024). Prognostic Impact of Heart Failure Pharmacotherapies in Acute Heart Failure: Strong Association in Mildly Reduced Ejection Fraction. European Journal of Preventive Cardiology, 31(11), 1361–1362. https://doi.org/10.1093/eurjpc/zwae162

Gianfredi, V., Nucci, D., Pennisi, F., Maggi, S., Veronese, N., & Soysal, P. (2025). Aging, longevity, and healthy aging: the public health approach. Aging Clinical and Experimental Research, 37(1), 125. https://doi.org/10.1007/s40520-025-03021-8

Gomera, R. T., van Hougenhouck-Tulleken, W., Brand, S. J., Van Niekerk, C., & Outhoff, K. (2026). Hypertension pharmacogenetics and limitations in Africa–a focus on the ACE, AGTR1 and CYP2C9 genes. Journal of Human Hypertension, 1-8. https://doi.org/10.1038/s41371-026-01121-0

Groote, P. de, Ennezat, P.-V., & Mouquet, F. (2007). Bisoprolol in The Treatment of Chronic Heart Failure. Vascular Health and Risk Management, 3, 1–10. https://www.tandfonline.com/doi/full/10.2147/vhrm.s12187371

Hassan, W., Nila, S. A., Ahmed, M., Okello, D. O., Maqbool, M., Dabas, M. M., Nour, M., Khan, S. M., Ansari, F., Anum, N., & Pervaiz, S. (2024). Comparative Efficacy and

Long-Term Outcomes of Beta-Blockers Alone or in Combination With Angiotensin-Converting Enzyme (ACE) Inhibitors in Chronic Heart Failure: A Systematic Review. Cureus. https://doi.org/10.7759/cureus.74329

Lund, L. H., Maggioni, A. P., Crespo-Leiro, M. G., Laroche, C., Gotsman, I., Pojskic, B., ... & Rosano, G. (2026). Outcomes of heart failure with reduced, mildly reduced, or preserved ejection fraction: the ESC HF III registry. European heart journal, ehaf1074. https://doi.org/10.1093/eurheartj/ehaf1074

Mancia, G., Kjeldsen, S. E., Kreutz, R., Pathak, A., Grassi, G., & Esler, M. (2022). Individualized beta-blocker treatment for high blood pressure dictated by medical comorbidities: indications beyond the 2018 European Society of Cardiology/European Society of Hypertension Guidelines. Hypertension, 79(6), 1153-1166. https://doi.org/10.1161/HYPERTENSIONAHA.122.19020

Matsumoto, S., Henderson, A. D., Shen, L., Kondo, T., Yang, M., Campbell, R. T., Anand, I. S., de Boer, R. A., Desai, A. S., Lam, C. S. P., Maggioni, A. P., Martinez, F. A., Packer, M., Redfield, M. M., Rouleau, J. L., Van Veldhuisen, D. J., Vaduganathan, M., Zannad, F., Zile, M. R., … McMurray, J. J. V. (2025). Beta-Blocker Use and Outcomes in Patients with Heart Failure and Mildly Reduced and Preserved Ejection Fraction. European Journal of Heart Failure, 27(1), 124–139. https://doi.org/10.1002/ejhf.3383

Milhem, F., Almur, O., Hajjeh, O., Bdair, M., Dahmas, A. M., Haddad, K. B., ... & AbuBaha, M. (2025). Advances and controversies in acute decompensated heart failure treatment: beta-blocker roles, emerging devices, and future directions. Annals of Medicine and Surgery, 87(9), 5696-5719. https://doi.org/10.1097/MS9.0000000000003592

Miura, S. I., Matsuo, Y., & Seumatsu, Y. (2025). Renin-angiotensin-aldosterone system and its relation to hypertension. Hypertension Research, 48(8), 2209-2217. https://doi.org/10.1038/s41440-025-02229-5

Mocan, D., Jipa, R., Jipa, D. A., Lala, R. I., Rasinar, F. C., Groza, I., ... & Puschita, M. (2025). Unveiling the systemic impact of congestion in heart failure: A narrative review of multisystem pathophysiology and clinical implications. Journal of Cardiovascular Development and Disease, 12(4), 124. https://doi.org/10.3390/jcdd12040124

Nasoufidou, A., Bantidos, M. G., Fyntanidou, B., Kofos, C., Stachteas, P., Arvanitaki, A., ... & Karagiannidis, E. (2025). Cardioprotective Mechanisms of Beta-Blockers in Myocardial Ischemia and Reperfusion: From Molecular Targets to Clinical Implications. International Journal of Molecular Sciences, 26(20), 9843. https://doi.org/10.3390/ijms26209843

Parizad, R., Hatwal, J., Taban Sadeghi, M., Brar, A., Desai, R., Batta, A., & Mohan, B. (2026). Clinical Advances in Heart Failure with Preserved Ejection Fraction: A Systematic Review of Therapeutic and Mechanistic Evidence. Vascular Health and Risk Management, 578698. https://doi.org/10.2147/VHRM.S578698

Patolia, H., Khan, M. S., Fonarow, G. C., Butler, J., & Greene, S. J. (2023). Implementing guideline-directed medical therapy for heart failure: JACC focus seminar 1/3. Journal of the American College of Cardiology, 82(6), 529-543.

Pugliatti, P., Trimarchi, G., Barocelli, F., Pizzino, F., Di Spigno, F., Tedeschi, A., ... & Di Bella, G. (2024). Advancing cardiac amyloidosis care through insights from cardiopulmonary exercise testing. Journal of Clinical Medicine, 13(23), 7285. https://doi.org/10.3390/jcm13237285

Rahayu, Z. T., Retnowati, E., & Kurniawan, G. (2025). Hubungan Profil Pasien Gagal Jantung terhadap Efektivitas Terapi Kombinasi Antihipertensi di Rawat Inap RSUD dr.

Loekmono Hadi Kudus. Jurnal Ilmiah Kedokteran Dan Kesehatan, 4(3), 535–545. https://doi.org/10.55606/klinik.v4i3.4838

Safiri, S., Asghari, K. M., & Sullman, M. J. (2023). The global burden of diseases and injuries among older adults. International Journal of Aging, 1(1), e16-e16. https://doi.org/10.34172/ija.2023.e16

Shahverdi, E., Shahverdi, A., Schneider, C., Lange, M., & Herda, L. R. (2026). Optimization and Real-World Implementation of Guideline-Directed Medical Therapy in Heart Failure With Reduced Ejection Fraction: A Contemporary Clinical Review. Cardiology Research, 17(2), 61. https://doi.org/10.14740/cr2195

Suleman, H., Shah, S., Babur, M. N., Wadood, A., Nisa, M. U., Ali, A., & Bashir, S. (2026). Effects of Respiratory Muscle Training on Cardiomyopathy Parameters and Quality of Life in Patients with Cardiomyopathy. The Healer Journal of Physiotherapy and Rehabilitation Sciences, 6(2), 1-10. https://doi.org/10.55735/kqhb7105

Tang, J., Wang, P., Liu, C., Peng, J., Liu, Y., & Ma, Q. (2025). Pharmacotherapy in Patients with Heart Failure with Reduced Ejection Fraction: A Systematic Review and Meta-Analysis. Chinese Medical Journal, 138(8), 925–933. https://doi.org/10.1097/CM9.0000000000003118

Tran, H. H. V., Thu, A., Brilhante, M., Twayana, A. R., Fuertes, A., Gonzalez, M., ... & Aronow, W. S. (2025). Evidence-Based Quality Improvement Strategies to Reduce 30-Day Readmission Rates in Heart Failure Patients. Cardiology in Review, 10-1097. https://doi.org/10.1097/CRD.0000000000001039

Yang, M. S., Abdallah, M. B., Bashir, Z., & Khalife, W. (2024). Heart Failure Beyond the Diagnosis: A Narrative Review of Patients' Perspectives on Daily Life and Challenges. Journal of clinical medicine, 13(23), 7278. https://doi.org/10.3390/jcm13237278

Zhou, W., Jin, S., Shen, F., & Zhang, X. (2026). Health Risks Among Rural Aging Populations in China: A Cross-Sectional Study of Knowledge, Attitudes, and Practices in Chronic Disease Management. Risk Management and Healthcare Policy, 1-17. https://doi.org/10.2147/RMHP.S569629