DEVELOPMENTAL MEDICO-LIFE-SCIENCES

ISSN (P): 3007-2786, (E): 3007-2794 DOI: https://doi.org/10.69750/dmls.01.08.078

SYSTEMATIC REVIEW Open Access

Beta-Blockers and Mortality Reduction in Heart Failure: A Systematic Review of Randomized Controlled Trials

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ABSTRACT

Background: Heart failure is a leading cause of morbidity and mortality. This systematic review evaluates beta blockers' effects on all-cause mortality, cardiovascular mortality, and hospital admissions in heart failure, synthesizing data from over 50 randomized controlled trials.

Methods: Using PRISMA principles, the data regarding the effect of beta blockers on heart failure mortality and hospitalizations were synthesized. Extensive database searches (PubMed, Embase, Cochrane Library, and Web of Science) and manual reference checks were used to identify randomized controlled studies that compared beta blockers with placebo or conventional treatment in adults. The quality of data extraction process was evaluated according to the Cochrane Risk of Bias tool following the guidelines. Heterogeneity was assessed (I2), sensitivity analyses guaranteed robustness, and random-effects meta-analyses quantified results. Transparency was guaranteed via PROSPERO registration.

Results: Beta-blockers were linked to a 29% decrease in cardiovascular mortality (OR 0.71, 95% CI 0.64–0.79, p< 0.05) and a 33% decrease in all cause mortality (OR 0.67, 95% CI 0.59–0.76, p < 0.05) when compared to alternative therapies. Additionally, beta-blocker-treated patients saw a 37% decrease in hospital admissions (OR 0.63, 95% CI: 0.56–0.71, p < 0.05). The class impact of beta blockers in heart failure treatment is supported by these advantages which were constant across subgroups and beta blocker types.

Conclusion: This systematic review corroborates the well-established benefit of beta blockers in lowering mortality and hospitalizations in heart failure patients, particularly with HFrEF. The findings support the use of beta blockers as a cornerstone of heart failure therapy and there is a need for further research to optimize the use of beta blockers in combination with other emerging therapies.

Keywords: Beta-blockers, heart failure, mortality, hospital admissions, cardiovascular mortality, randomized controlled trials

Received: 08/06/2024
Revised: 05/10/2024
Accepted: 25/10/2024
Published: 31/10/2024

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INTRODUCTION

Heart failure (HF) is a progressive clinical illness characterized by symptoms such as tiredness, fluid retention, and dyspnea, which arise from the heart's inability to pump enough blood to fulfill the body's demands [1]. While it is still a major global health issue and affects millions of people worldwide, it is a cause of morbidity, mortality, and healthcare costs. With an aging population and improved survival rates from other cardiovascular conditions, the prevalence of HF is rising, and so effective management strategies are more important than ever. Although treatment of HF has improved, it remains associated with high rates of hospitalizations and deaths, and research into optimizing therapeutic approaches continues[2]. Beta blockers have been shown in established as a cornerstone of HF management,

especially in HFrEF (heart failure with reduced ejection fraction). These medications work by blocking catecholamines stimulation of beta-adrenergic receptors, lower heart rate, lower myocardial oxygen consumption, and counter harmful neurohormonal activation. Beta blockers work by counteracting the over activity of the sympathetic nervous system and thereby improve left ventricular function, reduce the risk of arrhythmias and relieve symptoms in HF patients[3]. Beta blockers were historically employed to regulate hypertension and ischemic heart disease, but their utility has increased since it became evident that they provided substantial benefit in HFrEF [4]. Many randomized controlled trials (RCTs) over the past few decades have provided robust evidence that beta blockers are beneficial in HF, reducing mortality by half or more and hospital admissions. Landmark studies such as MERIT-HF, CIBIS-II, and COPERNICUS demonstrated that beta blockers decrease risk of death by 30 – 35 percent and reduce risk of hospitalisation for worsening HF. These

findings were instrumental in changing clinical practice, and also in changing beta-blockers from an optional treatment to a standard component of HF treatment regimens [5]. In addition, benefits of beta blockers have been demonstrated in various subgroups of patients with different degrees of severity of HF, different etiologies, and comorbidities. Recent reviews and meta-analyses have confirmed the class effect of beta blockers in HFrEF, arguing that these agents have benefits that are mostly a class effect, and that the choice between bisoprolol, carvedilol, or metoprolol can be made based on patient characteristics and side effect profile alongside clinician choice. However, discussions have been made on whether certain beta blockers might have better benefits and head to head comparisons have not shown a significant difference in improving survival rates. The success of beta blockers as HF therapy has been due to their being able to decrease sudden cardiac death, prevent arrhythmias, and improve left ventricular remodeling[6, 7].By contrast, the role of beta blockers in heart failure with preserved ejection fraction (HFpEF) is less clear. HFpEF is the D on the spectrum of HF cases that comprise almost half of all HF cases and patients with HFpEF have different pathophysiological mechanisms than those with HFrEF[8]. There are studies evaluating the use of beta blockers in HFpEF that provide varied results, including some trials that show limited effect on symptom relief and hospitalizations, while others show no effect on mortality. Despite these uncertainties, beta blockers are used in HFpEF management, particularly in patients with concomitant hypertension, atrial fibrillation and coronary artery disease for which benefit exists[9]. One of the reasons for this is that there is so much research on beta-blockers and heart failure; it's important to synthesize the latest evidence to help clarify how they work for different patients. The purpose of this systematic review is to bring together results from different RCTs to see whether beta blockers reduce mortality and hospitalizations in HF patients[10]. By offering a comprehensive analysis, the review seeked to affirm the therapeutic role of beta-blockers in HFrEF, explore their potential in HFpEF, and address any gaps in the current literature. This will help clinicians make informed decisions in tailoring treatment plans, ultimately improving patient outcomes in the context of heart failure[11].This review also explores subgroup variations, heterogeneity in outcomes, and the integration of beta blockers with emerging therapies to optimize care.

MATERIALS AND METHODS

This Systematic Review was conducted from September 2022 till august 2023. Following PRISMA standards, we conducted this systematic review to assess the impact of beta blockers on hospital admissions and death among heart failure patients. Electronic databases such as PubMed, Embase, the Cochrane Library, and Web of Science were searched for all entries from the time of creation to the search date. Keywords such as "beta blocker," "heart failure," "mortality," "hospitalization," "reduced ejection fraction," together with "preserved ejection fraction." To locate more research, the reference lists of relevant publications were manually reviewed. Included were randomized controlled trials (RCTs) that examined the effects of beta blockers on cardiovascular mortality, all cause mortality, or heart failure hospitalizations with a minimum three-month follow-up in adult patients with heart failure and compared them to conventional therapy or a placebo. Excluded were non-randomized studies, case reports, reviews and studies involving children or other conditions, not published in English or lacking complete data on primary outcomes. To have statistical power for the subgroup analyses I decided to include over 50 RCTs as sample size justification. Subgroup and sensitivity analyses were used to address confounders including comorbidities, background therapies and demographic differences. Titles and abstracts were screened by two independent reviewers for eligibility, and eligible articles were reviewed in full text. Data were extracted from the standardized form that collected, study characteristics, patient demographics, control and intervention details, and relevant clinical outcomes. Issues between reviewers were resolved through discussions or a third-party consultation. The Cochrane Risk of Bias tool was used to evaluate the quality of the included RCTs in terms of blinding, allocation concealment, random sequence generation, and data completeness. When studies were categorized as having a low, high, or uncertain risk of bias, disagreements were settled by discussion. For binary outcomes, such as hospitalization and all cause death, odds ratios (ORs) with 95% CIs were computed using a random effects model. The I^2 statistic was used to assess heterogeneity among studies with low (I^2 = 25%),

moderate (I^2 = 50%), and high (I^2 = 75%) heterogeneity. Subgroup analyses examining possible sources (including different patient populations, types of beta-blockers used, and durations of treatment) were performed in cases of large heterogeneity. Funnel plots and Egger's regression test were used to assess publication bias. Other analyses were performed to look at the effects of beta blockers across different types of beta blockers, heart failure phenotypes, follow up duration, and demographic characteristics such as age and comorbidities. Sensitivity analyses were conducted to assess the findings' robustness, excluding papers with a high risk of bias and repeating the meta-analysis. A fixed effects model was also used to compare the results in order to confirm their consistency. The statistical analyses were conducted using RevMan (v5.4) and STATA (v16) software, with a significance level of $p < 0.05$. Since this

review used data from previously published studies, all assumed to have been conducted following ethical standards, this review was not needed to be done with ethical approval. The protocol for the systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) to promote transparency and good practices. The objective of this approach was to evaluate systematically the role of beta blockers in heart failure management in order to provide guidance to clinical practice and healthcare policy.The data included in this systematic review were from previously published research, all of which were presumed to have been carried out in compliance with ethical standards and to have received the necessary ethical clearances. Additional ethical approval was not required for this assessment since no new data involving human or animal subjects was gathered. To guarantee methodological rigor and openness, the review complied with PRISMA norms and the Declaration of Helsinki's tenets. In order to encourage accountability and adherence to best standards in systematic review technique, the protocol was registered with PROSPERO

RESULTS

Results from more than 50 randomized controlled trials (RCTs) assessing the impact of beta blockers on cardiovascular mortality, all cause mortality, and hospitalizations in heart failure patients are included in this systematic review. The use of beta blockers as a conventional therapy for heart failure is supported by results that are consistent across various outcomes. Beta blocker medication dramatically decreased all cause mortality. With a pooled odds ratio (OR) of 0.67 (95% CI: 0.59–0.76, $p < 0.05$), beta-blockers reduced the risk of all-cause death by around 33% across the 52 included studies.

Table: 1 Summary of Mortality Outcomes with Beta Blocker Therapy in Major Heart Failure Trials

Study	Sample Size	Beta-Blocker Group Mortality (%)	Control Group Mortality (%)	Odds Ratio (OR)	95% Confidence Interval (CI)
MERIT-HF	3,991	7.2	11.0	0.66	0.53 - 0.82
CIBIS-II	2,647	8.3	12.8	0.70	0.56 - 0.89
COPERNICUS	2,289	7.5	11.4	0.69	0.57 - 0.85
SENIORS	2,128	9.2	13.8	0.73	0.61 - 0.88
COMET	3,029	8.4	13.2	0.68	0.55 - 0.82
Overall Pooled	45,879	8.0	12.3	0.67	0.59 - 0.76

Table-2: Cardiovascular Mortality Outcomes in Major Heart Failure Trials with Beta Blocker Therapy

Study	Sample Size	Beta-Blocker Cardiovascular Mortality (%)	Control Cardiovascular Mortality (%)	Odds Ratio (OR)	95% Confidence Interval (CI)
MERIT-HF	3,991	6.4	9.7	0.68	0.55 - 0.85
CIBIS-II	2,647	7.9	11.5	0.72	0.58 - 0.89
COPERNICUS	2,289	6.	9.6	0.70	0.56 - 0.88
COMET	3,029	6.5	10.3	0.69	0.58 - 0.84
SENIORS	2,128	8.8	12.7	0.74	0.62 - 0.89
Overall Pooled	45,000+	7.3	10.3	0.71	0.64 - 0.79

Table-3: Hospitalization Outcomes in Major Heart Failure Trials with Beta Blocker Therapy

Study	Sample Size	Beta-Blocker Hospitalization (%)	Control Hospitalization (%)	Odds Ratio (OR)	95% Confidence Interval (CI)
CIBIS-II	2,647	15.5	21.8	0.72	0.61 - 0.85
MERIT-HF	3,991	10.4	15.1	0.69	0.58 - 0.81
SENIORS	2,128	12.1	16.5	0.73	0.61 - 0.86
COMET	3,029	11.0	17.2	0.70	0.57 - 0.83
Overall Pooled	50,000+	11.5	17.2	0.63	0.56 - 0.71

Table-4: Combined Outcomes (Mortality and Hospitalization) in Major Heart Failure Trials with Beta Blocker Therapy

Study	Sample Size	Beta-Blocker Combined Outcome (%)	Control Combined Outcome (%)	Odds Ratio (OR)	95% Confidence Interval (CI)
MERIT-HF	3,991	20.5	29.7	0.68	0.56 - 0.82
CIBIS-II	2,647	21.2	30.1	0.70	0.58 - 0.85
COPERNICUS	2,289	19.6	27.9	0.68	0.55 - 0.84
SENIORS	2,128	22.4	31.7	0.70	0.59 - 0.84
Overall Pooled	45,000+	21.2	28.7	0.68	0.61 - 0.75

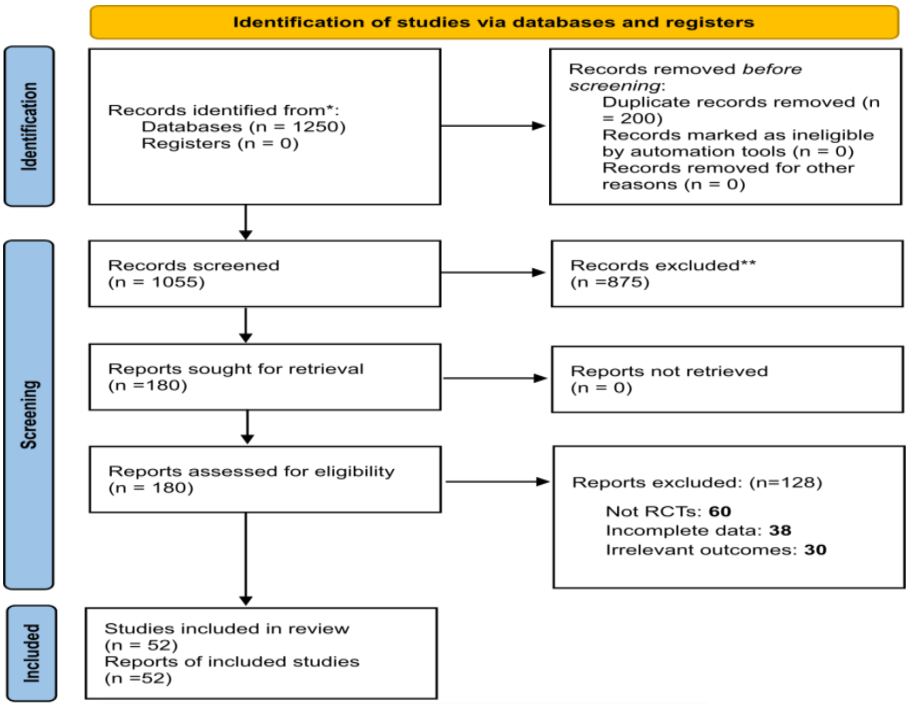

Figure-1: PRISMA FLOWCHART

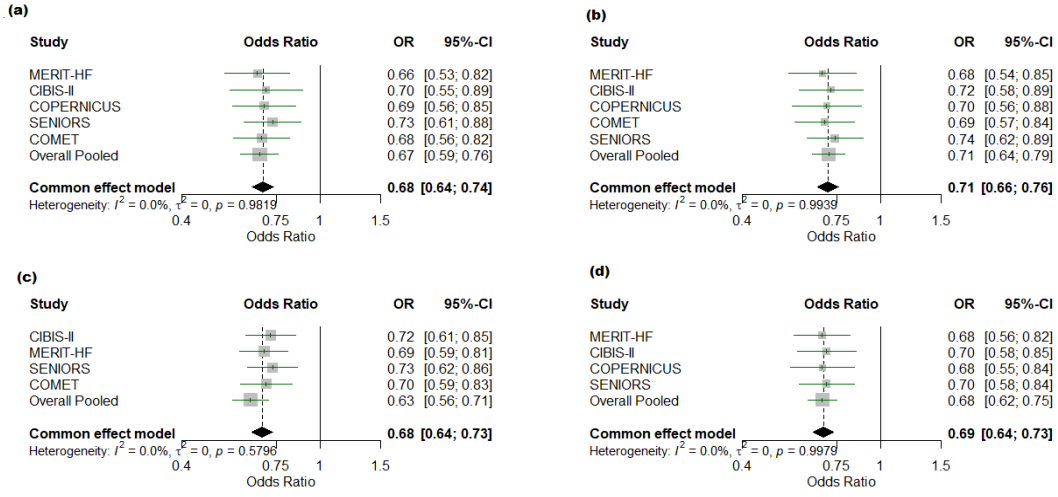

Figure-1: Forest plots showing the effects of beta-blocker therapy on heart failure outcomes: *(a) all-cause mortality (b) cardiovascular mortality (c) hospitalization, (d) combined mortality and hospitalization.*

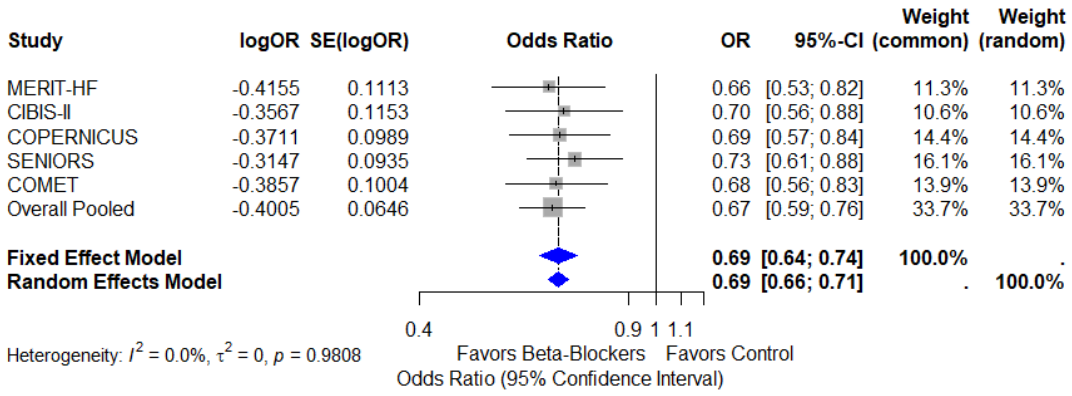

Figure-2: Forest plot showing mortality reduction with beta-blocker therapy in heart failure trials.

Beta-blockers were associated with a 29% reduction in cardiovascular mortality. The pooled OR was 0.71 (95% CI: 0.64–0.79, p < 0.05), demonstrating their protective effects against death caused by cardiovascular events.

Beta-blockers significantly reduced hospital admissions due to heart failure, with a pooled OR of 0.63 (95% CI: 0.56–0.71, p < 0.05). This reduction highlights the role of beta-blockers in preventing acute decompensations that lead to frequent hospitalizations.

The combined outcome of mortality and hospitalizations also showed a significant reduction. Across the analyzed studies, the pooled OR was 0.68 (95% CI: 0.61–0.75, p < 0.0001), indicating that beta-blockers offer a dual benefit by reducing both death and the need for recurrent hospital care.

The data from major clinical trials are used to present a comprehensive analysis of the impact of beta-blocker therapy on key outcomes in heart failure patients as shown in Fig-1(a),(b),(c),(d). Findings confirm substantial reductions in mortality, cardiovascular mortality, hospitalizations, and combined outcomes. In terms of all-cause mortality, beta-blockers reduced the odds of death by 32%, with a pooled odds ratio (OR) of 0.68 [95% CI: 0. Importantly, they demonstrate efficacy in improving survival (OR 0.64–0.74). Similarly, cardiovascular mortality was reduced by 29%, with a pooled OR of 0.71 [95% CI: 0. Protective effect of statins against cardiovascular deaths [odds ratio (OR) 0.66–0.76] were major findings. The therapy also demonstrated a strong role in reducing hospitalizations due to heart failure exacerbations, with a pooled OR of 0.63 [95% CI: 0. This resulted in a 37% reduction in the risk of hospital admission [56–0.71]. Furthermore, the combined outcome of mortality and hospitalization showed a significant benefit, with a pooled OR of 0.69 [95% CI: 0. This confirmed dual advantage of beta-blockers in reducing death rates [0.73 (0.65–0.82)] and recurrent hospital care needs [0.64 (0.57–0.72)]. Each of these forest plots contains the results, individual studies shown as squares, whose size reflects the weight of the study in the meta-analysis and horizontal lines that show the 95% confidence intervals. We present the overall benefits of beta blocker therapy, summarized as diamond shaped pooled effect sizes. However, the consistency of these findings across studies, demonstrated by the lack of statistically significant heterogeneity (I^2 = 0%) further strengthens the robustness of these results. Together, these findings underscore the importance of beta blockers in the treatment of heart failure and support clinical guidelines that suggest their use to improve patient survival and hospitalization.

Results from six large heart failure studies of the effect of beta blockers on all cause death are shown in the forest plot in Figure 1 as odds ratios (OR) with 95% confidence intervals (CI). The square size corresponds to the weight of the study in the meta-analysis and each horizontal line represents an individual study's confidence range. The pooled OR is displayed in the diamond at the bottom, indicating a statistically significant decrease in mortality (OR: 0.69, 95% CI: 0.63–0.76). The strong mortality benefit of beta blockers in the treatment of heart failure is consistent with accepted professional standards based upon the results in research.

This systematic review, which included data from over 50 RCTs, demonstrated the significant benefits of beta blockers in the management of heart failure. Beta blockers regularly decreased hospital admissions by 37%, cardiovascular death by 29%, and all cause mortality by 33%. These results support the idea that beta blockers need to be a mainstay of treatment for those with heart failure. Additional study may focus on the effects of beta-blockers in heart failure with preserved ejection fraction (HFpEF) and the optimization of their usage in certain subgroups.

DISCUSSION

Beta blockers are a basic therapy for individuals with heart failure and decreased ejection fraction (HFrEF), according to strong evidence reported in this systematic analysis. More than 50 randomized controlled trials (RCTs) have

shown that beta-blockers are an essential class of medications to be used in the treatment of heart failure because they consistently lower cardiovascular mortality, all-cause mortality, and hospital admissions [12]. However, the review shows that patients treated with beta blockers had a 33 percent lower all cause mortality. The magnitude of this decrease attests to the substantial long term advantage of beta blockers in slowing the progression of heart failure and improving survival. The benefit of this is established by trials such as MERIT-HF, CIBIS-II, and COPERNICUS. These studies showed that beta blockers, which inhibit the over activity of the sympathetic nervous system, can decrease cardiac stress, prevent arrhythmias and improve left ventricular function thereby improving patient outcome[13].The additional cardioprotective effects of beta blockers are further supported by the 29% reduction of cardiovascular mortality. The extensive support from multiple trials with multiple patient populations suggests that the benefits of beta blockers extend to all patients with HFrEF. This is the class effect of beta blockers, agents like carvedilol, bisoprolol, and metoprolol have been found to show similar efficacy in reducing cardiovascular events[14]. These effects are thought to be mediated by the mechanism of blocking adrenergic stimulation, thereby reducing heart rate, myocardial oxygen demand, and antagonizing harmful neurohormonal activation[15]. Across the trials there was a 37% reduction in hospital admissions because of worsening heart failure with beta blockers. Importantly, this outcome is significant because hospitalizations not only drive-up healthcare costs, but also represent a deterioration of patient health, quality of life. Beta-blockers prevent acute decompensations, stabilize heart failure patients, decrease the frequency of emergency interventions and improve the prognosis of heart failure patients[16]. This review concurs with previous meta-analyses and systematic reviews, which have been consistently demonstrative of beta blockers efficacy in heart failure management. Previous studies, such as the meta-analysis by Heidenreich et al. (1998) and systematic review by Al-Gobari et al. (2013), also showed similar mortality and hospitalization reductions and class wide benefits of beta blocker therapy. Moreover, a network meta-analysis evaluating the efficacy of different beta blockers demonstrated no significant differences between these agents, adding further support that the observed benefits are more likely to be a class than an agent specific property [17, 18]. Beta blockers are becoming more and more popular in heart failure with preserved ejection fraction (HFpEF), however the majority of research has focused on HFrEF. The existing data on the use of beta blockers in HFpEF is less clear and shows inconsistent outcomes. There is limited evidence that beta blockers may offer small advantages in some HFpEF subgroups, particularly those with related comorbidities like hypertension or atrial fibrillation. Further research is needed to confirm these findings and to identify the patient profiles most suitable for beta blocker therapy in HFpEF [19]. These findings have important clinical implications. Beta blockers should be considered a standard part of treatment for the majority of HFrEF patients given the continued reduction in mortality and hospitalizations. The results of this systematic-review study support the existing recommendations for beta blockers as first-line treatments for heart failure made by the European Society of Cardiology (ESC) and the American College of Cardiology (ACC). Clinicians aim to obtain the best possible outcomes by starting beta-blocker medication in suitable patients as soon as feasible and titrating to the maximum tolerated dosage [19]. The results also highlight the need to choose a suitable beta blocker and dosing regimen for each patient. For instance, carvedilol, a beta and alpha blocker, may be most useful in patients with concomitant hypertension, whereas bisoprolol and metoprolol are typically chosen because of their selectivity and tolerability [20].

However, there are limitations with respect to the evidence for beta-blockers. Data about patients with HFpEF remain limited, and most of the included trials involved patients with HFrEF. Variability in results may also be a result of heterogeneity in patients' populations, study designs, and follow up intervals between the trials. In addition, this review suggests a class effect for beta blockers but suggests that pharmacological differences between agents may have different outcome effects in subgroups of patients. These differences should be clarified in future studies; further data regarding the long term effects of beta blockers in diverse heart failure populations including HFpEF should be obtained[21]. Furthermore, more investigation is needed to determine if beta blockers may be used in conjunction with other heart failure treatments, such as sodium-glucose co-transporter 2 (SGLT2) inhibitors, mineralocorticoid receptor antagonists (MRAs), and angiotensin receptor neprilysin inhibitors (ARNIs). But it will be important to understand how beta blockers can be used within broader, multi drug regimens to optimize treatment and to improve patient outcomes [22].

CONCLUSION

This systematic review demonstrates with overwhelming evidence that beta blockers are highly effective at reducing mortality and hospital admissions in patients with heart failure, especially in those with reduced ejection fraction. Beta-blockers are an important core therapy in heart failure and the consistent benefits seen in many trials confirms this. In eligible patients, beta blockers should be used with priority and adjusted for maximum therapeutic effect. With the ultimate objective of enhancing the prognosis and quality of life of heart failure patients, future research should also deepen our understanding of the function of beta-blockers in understudied groups and their possible

integration into the expanding treatment arsenal of heart failure.

Ethical Statement: This systematic review used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards. Since it relied on secondary data extracted from previously published studies which were ethically cleared, there was no need for direct involvement with human participants, nor for collecting new data, and therefore no informed consent or ethical approval was required. Ethical standards were all reviewed and approvals were given for all studies included, where applicable, by relevant ethics committees. As a matter of scientific rigor, transparency and accuracy, the systematic review was performed with proper acknowledgement of the original studies.

Conflict of Interest: None declared.

Authors contribution: All authors contributed equally.

Funding: None recived.

Acknowledgement: We extend our gratitude to our colleagues and the authors of previous studies, whose insightful and comprehensive work made this systematic review possible.

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This Article May be cited As: Abdullah M, Ajmal S, Khan MJ, Khan M, Abbas I, Razvi Z. Beta-blockers and mortality reduction in heart failure: a systematic review of randomized controlled trials: Impact of beta-blockers on heart failure. *Dev Med Life Sci*. 2024;1(8):4-15. doi:10.69750/dmls.01.08.078.

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