

The Association of Metoprolol Use With Outcomes in Heart Failure With Preserved Ejection Fraction (HFpEF): A Propensity Score-Matched Cohort Study

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Abstract

This cohort study investigates the comparative health outcomes of patients with heart failure with preserved ejection fraction (HFpEF) treated with and without metoprolol, a commonly prescribed beta-blocker. Utilizing data from the TriNetX US Collaborative Network comprising 70 healthcare organizations, the study defines two propensity score-matched cohorts: HFpEF patients without metoprolol and those receiving metoprolol, excluding individuals with atrial fibrillation. Key outcomes assessed include mortality, HF exacerbation, and incidence of chronic kidney disease (CKD). Statistical analyses, including risk ratios (RRs) and Kaplan-Meier survival estimates, were employed to evaluate differences between cohorts. All RRs are reported for the non-metoprolol cohort (Cohort 1) relative to the metoprolol cohort (Cohort 2, reference group), so that an RR below 1.00 denotes a lower risk of the outcome in patients not treated with metoprolol, and all absolute risk differences (ARDs) are calculated as the event rate in the metoprolol cohort minus the event rate in the non-metoprolol cohort.

The results demonstrate that HFpEF patients not treated with metoprolol had comparatively lower risks of mortality (15.51% vs. 18.54%; ARD: 3.03%; RR: 0.886, 95% confidence interval (CI) 0.868-0.903), HF exacerbations (6.76% vs. 8.90%; ARD: 2.14%; RR: 0.79, 95% CI: 0.765-0.815), and CKD (11.80% vs. 14.49%; ARD: 2.69%; RR: 0.838, 95% CI: 0.816-0.861) compared to those receiving metoprolol. Survival analysis further supports this association, indicating significantly higher survival probabilities in the non-metoprolol cohort. These findings suggest that metoprolol was associated with increased mortality in HFpEF patients. There may be some increased risk in HFpEF patients; however, given the retrospective observational design of the study, these findings indicate an association rather than a causal relationship, and residual confounding cannot be ruled out. Further randomized controlled trials are needed to clarify the effects of metoprolol and optimize management strategies for this complex patient population.

Categories: Cardiology, Internal Medicine

Keywords: heart failure, hfpef, metoprolol, morbidity, mortality

Introduction

Heart failure with preserved ejection fraction (HFpEF) represents a significant challenge in cardiovascular medicine due to its complex pathophysiology and the limited availability of effective therapies compared with those for heart failure with reduced ejection fraction (HFrEF) [1]. HFpEF is characterized by preserved contractile function but impaired left ventricular filling, leading to symptoms of heart failure, such as dyspnea and fatigue, despite a normal ejection fraction [2]. The use of beta-blockers, such as metoprolol, has been explored as a potential treatment because of their ability to reduce heart rate and potentially improve diastolic function [3]. Although the mortality benefits of beta-blockers, particularly metoprolol, have been established in HFrEF through landmark trials such as MERIT-HF, their role in HFpEF remains controversial, with limited evidence supporting their routine use in this population [3].

This study aimed to compare health outcomes in patients with HFpEF treated with and without metoprolol using a retrospective, propensity score-matched cohort design. The study evaluated key health outcomes, including all-cause mortality, HF exacerbation, and chronic kidney disease (CKD), across two distinct cohorts. Using various analytical methods, including measures of association and survival analysis, this research sought to elucidate the potential benefits and risks associated with metoprolol use in patients with HFpEF. Given the rising prevalence of HFpEF, which currently accounts for approximately half of all heart failure cases, understanding the effectiveness of metoprolol may provide valuable insights for clinicians managing patients with this condition [4,5]. By comparing propensity score-matched cohorts, this study sought to minimize the influence of confounding variables and provide more reliable estimates of the association between metoprolol use and health outcomes in patients with HFpEF.

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Materials And Methods

Study design and time frame

This retrospective, propensity score-matched cohort study utilized de-identified electronic health record data from the TriNetX US Collaborative Network, which comprises records from 70 healthcare organizations. The study period extended from January 1, 2005, through December 31, 2023. Patients were followed from the index date, defined as the date of their first qualifying diagnosis of diastolic heart failure, until the occurrence of a primary endpoint, death, loss to follow-up, or the end of the study period, whichever occurred first.

Inclusion and exclusion criteria

Patients were included if they were aged 18 years or older and had a confirmed diagnosis of diastolic HF in acute exacerbation (ICD-10 code I50.3x) with a documented left ventricular ejection fraction (LVEF) $\geq$ 50% within 12 months of the index diagnosis. Two cohorts were defined: Cohort 1 (HFpEF without metoprolol) included patients with diastolic HF who had no documented prescription for metoprolol at any point during the study period, and Cohort 2 (metoprolol HFpEF) included patients with diastolic HF who had at least one documented prescription for metoprolol within 90 days of the index diagnosis. Exclusion criteria for both cohorts included (1) concurrent diagnosis of atrial fibrillation or atrial flutter (ICD-10 I48.x) at any time before or within 30 days after the index date; (2) diagnosis of other supraventricular or ventricular tachyarrhythmias; (3) history of heart transplantation or left ventricular assist device implantation; (4) active malignancy at the time of index diagnosis; and (5) fewer than two clinical encounters recorded in the database during the follow-up period. HF exacerbation was defined as a hospital admission after diagnosis of HFpEF.

Cohort definitions and data collection

Cohort 1, referred to as HFpEF without metoprolol, comprised patients diagnosed with diastolic HF who met all inclusion criteria and none of the exclusion criteria, and who were not treated with metoprolol. This cohort captures a broad spectrum of patients with diastolic dysfunction, free of potential confounding effects due to metoprolol treatment. Cohort 2, referred to as metoprolol HFpEF, included patients with diastolic HF who met all inclusion criteria and none of the exclusion criteria, and who were receiving metoprolol. This group enabled the assessment of health outcomes associated with metoprolol use in comparison with those in patients who were not receiving this beta-blocker. Data for both cohorts were collected through structured queries of the TriNetX US Collaborative Network. Comprehensive data collection, including demographics, medication history, comorbidities, and health outcomes, facilitated a longitudinal view of patient health, providing a basis for meaningful comparative analysis.

Propensity score matching

A critical component of the methodology is propensity score matching, which enhances the comparability of the two cohorts by accounting for potential confounding factors such as age, sex, race/ethnicity, BMI, hypertension, diabetes mellitus, hyperlipidemia, and coronary artery disease. Propensity scores were estimated using multivariable logistic regression, and patients were matched 1:1 using nearest-neighbor matching with a caliper width of 0.2 standard deviations (SDs) of the logit of the propensity score. This matching process ensures that the outcomes attributed to metoprolol use are not confounded by baseline differences, allowing for a more accurate estimation of treatment effects [6].

Matching produced two cohorts of identical size, each comprising 121,591 patients. Balance between the matched cohorts was assessed with standardized mean differences (SMD), with an absolute SMD below 0.10 taken to indicate adequate balance; SMDs rather than p-values were used for this purpose because, at this sample size, trivial absolute differences generate nominally significant p-values. All matched covariates met this threshold, the largest absolute SMD being 0.012 for age. The number of patients contributing to each outcome analysis is smaller than, and differs slightly between, the matched cohorts of 121,591. This is not a consequence of unequal matching: each outcome analysis was restricted to patients who did not already have the outcome of interest recorded at or before the index date and who had at least one follow-up encounter after the index date. These outcome-specific exclusions were applied separately for all-cause mortality, heart failure exacerbation, and chronic kidney disease, and they account for the unequal analytic denominators reported in the Results section.

Statistical analysis

The primary outcomes evaluated in this study included all-cause mortality, HF exacerbation rates, and incidence of CKD. CKD was defined as a diagnosis of CKD of all stages (I through V). Risk ratios (RRs) with 95% confidence intervals (CIs) were calculated to quantify the relative incidence of each outcome between cohorts. Throughout this manuscript, every RR is expressed with the metoprolol cohort (Cohort 2) as the reference group and the non-metoprolol cohort (Cohort 1) as the index group; an RR below 1.00 therefore denotes a lower risk of the outcome among patients not treated with metoprolol, and no RR is reported in the opposite orientation.

Absolute risk differences (ARDs) were calculated as the event rate in the metoprolol cohort minus the event rate in the non-metoprolol cohort, so that a positive value denotes excess absolute risk with metoprolol. Survival analysis was performed using Kaplan-Meier estimates, and between-group differences in survival were assessed using the log-rank test. Hazard ratios (HRs) with 95% CI were estimated using Cox proportional hazards regression. All statistical tests were two-sided, and a p-value of less than 0.05 was considered statistically significant. Analyses were performed using R version 4.3 (R Foundation for Statistical Computing, Vienna, Austria).

Handling of immortal time bias

Because exposure status was defined by a metoprolol prescription recorded within 90 days after the index diagnosis of diastolic HF, patients allocated to Cohort 2 had, by definition, to remain alive and in follow-up long enough for that prescription to be issued. The interval between the index date and the first metoprolol prescription therefore constitutes immortal person-time. Two features of the design limit its influence. First, time zero was defined identically in both cohorts as the date of the first qualifying diagnosis of diastolic HF, so that follow-up began at the same clinical milestone in each group rather than at the date of first prescription, and patients were not classified based on events occurring after time zero in the comparator arm. Second, the exposure ascertainment window was capped at 90 days, which bounds the maximum immortal person-time that the metoprolol cohort can accrue to that interval.

Exposure was nevertheless treated as a fixed characteristic assigned at baseline rather than as a time-varying covariate, and no landmark analysis excluding events occurring within the first 90 days of follow-up was performed. Consequently, residual immortal time bias remains a potential concern. Its direction, however, is predictable. Immortal time bias systematically favors the treated group because event-free survival time preceding treatment initiation is attributed to the treated cohort. This bias inflates survival estimates and median survival in the metoprolol cohort and shifts the RRs for the non-metoprolol cohort upward, toward or above 1.00. The associations reported below show the opposite pattern, with higher event rates, lower survival probabilities, and shorter median survival in the metoprolol cohort. Therefore, immortal time bias is unlikely to explain these findings and, if present, would tend to attenuate the observed associations. Median survival time is particularly sensitive to the accrual of immortal person-time and is accordingly reported descriptively rather than as a formal effect estimate.

Results

All-cause mortality

After propensity score matching, 121,591 patients were included in Cohort 1 (HFpEF without metoprolol) and 121,591 patients in Cohort 2 (metoprolol HFpEF) for the mortality analysis. Cohort characteristics after matching are presented in Table 1.

Characteristic	Cohort 1: HFpEF without metoprolol (n = 121,591)	Cohort 2: metoprolol HFpEF (n = 121,591)	P-value	Std. mean difference
Age, years, mean $\pm$ SD	59.7 $\pm$ 9.9	59.8 $\pm$ 9.9	0.003	0.012
Age, years, median (IQR)	62 (13)	62 (13)	—	—
Age at index, years, mean $\pm$ SD	54.5 $\pm$ 9.1	54.6 $\pm$ 9.2	0.004	0.012
Age at index, years, median (IQR)	57 (12)	57 (12)	—	—
Sex, n (%)				
Female	63,710 (52.4)	63,664 (52.4)	0.852	0.001
Male	57,847 (47.6)	57,890 (47.6)	0.861	0.001
Race, n (%)				
White	72,541 (59.7)	72,650 (59.7)	0.652	0.002
Black or African American	36,667 (30.2)	36,290 (29.8)	0.095	0.007
Asian	2,469 (2.0)	2,486 (2.0)	0.807	0.001
Native Hawaiian or Other Pacific Islander	1,050 (0.9)	985 (0.8)	0.148	0.006
American Indian or Alaska Native	1,003 (0.8)	1,042 (0.9)	0.386	0.004
Other race	3,079 (2.5)	3,221 (2.6)	0.07	0.007
Unknown race	4,782 (3.9)	4,917 (4.0)	0.162	0.006
Ethnicity, n (%)				
Not Hispanic or Latino	89,894 (73.9)	89,488 (73.6)	0.061	0.008
Hispanic or Latino	10,484 (8.6)	10,390 (8.5)	0.496	0.003
Unknown ethnicity	21,213 (17.4)	21,713 (17.9)	0.008	0.011

TABLE 1: Cohort characteristics after matching

Baseline characteristics of the two cohorts after 1:1 propensity score matching. Matching produced cohorts of identical size (n = 121,591 in each). Continuous variables are shown as mean $\pm$ SD and median (IQR); categorical variables as n (%). P-values are derived from independent-samples t-tests for continuous variables and chi-square tests for categorical variables. Standardized mean differences are reported for every matched covariate; an absolute value below 0.10 indicates adequate balance. All standardized mean differences were $\leq$ 0.012, confirming close balance despite the nominally significant p-values for age and unknown ethnicity, which reflect the very large sample size rather than a clinically meaningful difference

HFpEF: heart failure with preserved ejection fraction; SD: standard deviation; IQR: interquartile range

The event rate for all-cause mortality was 15.51% (n = 18,787) in Cohort 1 and 18.54% (n = 22,385) in Cohort 2, yielding an RR of 0.886 (95% CI: 0.868–0.903; p < 0.001) favoring the non-metoprolol group. Analysis demonstrated higher survival probability in Cohort 1 (43.27%) compared with Cohort 2 (43.19%). The median survival time for these patients was higher in Cohort 1; however, this is likely confounded by immortal time bias (Table 2). The log-rank test confirmed a statistically significant difference between survival curves (p < 0.001). This all points towards an association with patients with HFpEF on metoprolol having a lower incidence of survival; however, given the retrospective observational design, the results should be interpreted cautiously because of potential confounding factors, including immortal time bias and differences in the underlying clinical characteristics and disease severity of patients between the cohorts.

Cohort	N	Events	Event rate (%)	Median survival (days)	Survival probability (%)	Risk ratio (95% CI)	P-value
Comparison 1: all-cause mortality							
HFpEF without metoprolol	121,073	18,787	15.51	6213	43.27	Ref.	—
Metoprolol HFpEF	120,690	22,385	18.54	5247	43.19	0.886 (0.868-0.903)	< 0.001
Comparison 2: heart failure exacerbation							
HFpEF without metoprolol	99,876	6,749	6.76	Not reached	80.44	Ref.	—
Metoprolol HFpEF	94,626	8,425	8.90	Not reached	74.91	0.79 (0.765-0.815)	< 0.001
Comparison 3: chronic kidney disease							
HFpEF without metoprolol	88,222	10,393	11.8	Not reached	56.41	Ref.	—
Metoprolol HFpEF	79,156	11,467	14.49	6,153	41.30	0.838 (0.816-0.861)	< 0.001
Log-rank test: p < 0.001 for all three comparisons							

TABLE 2: Comparative outcomes and survival analysis of HFpEF patients with and without metoprolol

All risk ratios are expressed for Cohort 1 (HFpEF without metoprolol) relative to Cohort 2 (metoprolol HFpEF), which serves as the reference group; a risk ratio below 1.00 therefore indicates a lower risk of the outcome in patients not treated with metoprolol. The corresponding absolute risk differences (event rate in Cohort 2 minus event rate in Cohort 1) are 3.03% for all-cause mortality, 2.14% for heart failure exacerbation, and 2.69% for chronic kidney disease. Analytic denominators are smaller than the matched cohort size of 121,591 and differ between cohorts because each analysis excluded patients with the outcome recorded at or before the index date and patients without post-index follow-up; the 1:1 match itself was exact. "Not reached" indicates that fewer than 50% of patients in the cohort experienced the endpoint during the study follow-up period, and median survival is reported descriptively because it is the measure most sensitive to residual immortal time bias

HFpEF: heart failure with preserved ejection fraction; CI: confidence interval

Heart failure exacerbation

For the HF exacerbation analysis, 99,876 patients were included in Cohort 1 and 94,626 in Cohort 2. HF exacerbation occurred in 6.76% (n = 6,749) of Cohort 1 patients and 8.90% (n = 8,425) of Cohort 2 patients. The risk ratio was 0.79 (95% CI: 0.765-0.815; p < 0.001), indicating a significantly lower rate of HF exacerbation among HFpEF patients not on metoprolol (Table 2). Once again, this points towards an association with metoprolol and HF exacerbation rather than a causative factor.

Chronic kidney disease

In the CKD analysis, 88,222 patients were included in Cohort 1 and 79,156 in Cohort 2. CKD was observed in 11.8% (n = 10,393) of Cohort 1 and 14.49% (n = 11,467) of Cohort 2, with an RR of 0.838 (95% CI: 0.816-0.861; p < 0.001). The survival rate was also higher in the non-metoprolol group; however, this could also be confounded by the underlying sickness of the populations included in this study, as direct patient data and stratification by CKD stage were not possible with this database. Regardless, in terms of CKD, there was a signal towards an association with metoprolol and CKD progression; however, this is a weak association due to the numerous confounders within this study that cannot be accounted for.

Across all three outcome comparisons, patients in the metoprolol cohort consistently demonstrated higher event rates, lower survival probabilities, and statistically significant risk ratios and hazard ratios compared with the non-metoprolol cohort. These findings highlight a possible pattern of increased risk associated with metoprolol use in HFpEF patients, although interpretation must account for potential residual confounding inherent to retrospective study designs of databases without direct access to patient data [4].

Discussion

The findings of this study raise important questions regarding the role of beta-blockers, such as metoprolol, in the management of HFpEF. Although these medications have traditionally been used to alleviate symptoms and control hypertension, their physiological effects on diastolic filling may not translate into substantial clinical benefits in patients with HFpEF, particularly in light of the higher event rates observed in Cohort 2 [7]. Previous randomized trials of beta-blockers in HFpEF, including the J-DHF trial, have failed to demonstrate a significant reduction in the composite endpoint of cardiovascular death and heart failure hospitalization [8]. Similarly, a meta-analysis by Zheng et al. found no mortality benefit associated with beta-blocker therapy in patients with HFpEF, although modest improvements in heart rate reduction were reported [9].

The outcomes observed in this study suggest that a thorough, individualized assessment is important when considering beta-blocker therapy in patients with HFpEF. The association between metoprolol use and adverse outcomes, including all-cause mortality, underscores the importance of patient-specific evaluation and consideration of alternative therapeutic strategies when clinically appropriate [5]. These findings are consistent with observational data from the OPTIMIZE-HF registry, which reported no clear benefit and the possibility of harm associated with beta-blocker use in hospitalized patients with HFpEF [10]. The 2023 ACC/AHA heart failure guidelines do not support the routine use of beta-blockers solely for the treatment of HFpEF in the absence of another indication, such as atrial fibrillation or coronary artery disease [11].

Importantly, this study used propensity score matching to improve the comparability of the two cohorts. By accounting for measured confounders, including age, sex, and baseline comorbidities, the matched cohort design helps reduce selection bias in observational comparisons [6]. However, propensity score matching cannot account for unmeasured confounders, and confounding by indication, whereby patients with more severe illness may be more likely to receive metoprolol, cannot be fully excluded. Another limitation is the potential for immortal time bias. Because metoprolol exposure was ascertained over the 90 days following the index diagnosis, patients in the metoprolol cohort had to survive that interval to be classified as exposed. As described in the Methods section, this bias generally favors the metoprolol cohort by attributing early event-free time to the exposed group.

Therefore, immortal time bias alone would not explain the higher event rates observed in the metoprolol cohort and could instead attenuate the observed associations. However, it complicates the interpretation of median survival estimates, which should be considered descriptive rather than definitive measures of treatment effect. A landmark analysis excluding events occurring within the first 90 days or an analysis treating metoprolol exposure as a time-varying covariate would help assess the extent of this potential bias and should be prioritized in future research. Prospective randomized controlled trials are needed to confirm these findings and clarify the role of metoprolol in HFpEF management.

The observation that patients receiving metoprolol had higher rates of CKD is also noteworthy. This finding may be considered in the context of reports describing beta-blocker-associated changes in renal hemodynamics, including reductions in renal blood flow [12]. However, whether these physiological effects contribute to the observed differences in CKD incidence remains uncertain, and the present study cannot establish such a mechanism. This finding warrants further investigation, particularly given the retrospective nature of the study and the potential influence of residual confounding. This issue is especially relevant in the context of emerging therapies such as sodium-glucose cotransporter-2 (SGLT2) inhibitors, which have demonstrated cardiorenal protective effects in patients with HFpEF [13].

Conclusions

This retrospective, propensity score-matched cohort study provides evidence that patients with HFpEF who were not treated with metoprolol had higher survival probabilities and lower incidences of HF exacerbation and CKD than those receiving metoprolol. The risk ratios for all three primary outcomes consistently favored the non-metoprolol cohort, with statistically significant differences supported by Kaplan-Meier survival analysis and log-rank testing. These findings suggest the need to reassess the routine use of metoprolol in patients with HFpEF who lack an independent indication for beta-blocker therapy. By employing these analytical methods, including survival and risk assessments, this study contributes to the ongoing discussion regarding effective HFpEF management. Clinicians should carefully weigh the potential benefits and risks of metoprolol use, considering patient-specific factors that may influence outcomes. Further research, including adequately powered randomized controlled trials, is essential to refine treatment strategies for HFpEF, particularly because the retrospective design of this study and the potential for residual confounding limit the ability to establish causal relationships between metoprolol use and the observed outcomes.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Chirag Lodha, Eric J. Basile

Acquisition, analysis, or interpretation of data: Chirag Lodha, Eric J. Basile

Drafting of the manuscript: Chirag Lodha, Eric J. Basile

Critical review of the manuscript for important intellectual content: Chirag Lodha, Eric J. Basile

Supervision: Chirag Lodha

Disclosures

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