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*Research Article*

# A Prospective Observational Analysis Comparing the Safety and Effectiveness of Beta Blockers in Heart Failure with Preserved Ejection Fraction (HFPEF) To Those with Heart Failure with Reduced Ejection Fraction (HFREF)

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**ABSTRACT**
**Aim:** To compare the effectiveness and safety of beta blockers in heart failure with reduced (HFrEF) and preserved ejection fraction (HFpEF) patients.
**Methods:** A six-month prospective study at Aware Gleneagles Hospital, Hyderabad, enrolled 100 patients (50 HFpEF, 50 HFrEF). Demographic data, clinical parameters, and medication use were collected and analyzed. Primary endpoints: vital signs, adverse events, and duration of hospital stay. Secondary outcomes: reduction in NT-proBNP, renal impairment, and drug interactions. Statistical analyses: t-tests, chi-square tests, and survival analysis.
**Results:** Bisoprolol showed maximum efficacy, decreasing NT-proBNP by 22% (HFpEF) and 30% (HFrEF), with lesser side effects and shorter hospitalizations (5.6 ± 1.8 days) compared to Metoprolol, Carvedilol, and Nebivolol.
**Conclusion:** Bisoprolol is the most efficacious beta blocker for HFpEF and HFrEF patients, enhancing outcomes and reducing side effects.

**Keywords:** HFpEF, HFrEF, Bisoprolol, Metoprolol, Carvedilol, Nebivolol.

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## INTRODUCTION

Heart failure (HF) occurs in more than 64 million individuals worldwide and is ejection fraction (EF)-based into HFrEF (EF ≤40%), HFpEF (EF ≥50%), and HFmrEF (EF 41-49%)[1]. HFrEF is characterized by reduced myocardial contractions, whereas HFpEF is characterized by abnormal ventricular relaxation, which is prevalent in older hypertensive patients[2]. Diagnosis is dependent on biomarkers such as NT-proBNP and imaging methods such as echocardiography[3].

Beta-blockers are an essential part of HF management by lowering sympathetic overstimulation and enhancing left ventricular function[4–5]. Metoprolol ($\beta_1$-selective) lowers heart rate and contractility[6], Carvedilol (nonselective β and $\alpha_1$ blocker) has vasodilatory and antioxidant properties[7], Bisoprolol ($\beta_1$-selective) maintains blood pressure well[8], and Nebivolol ($\beta_1$-selective with vasodilatory activity) increases nitric

oxide release[9]. Their administration needs to be cautious in asthma, bradycardia, or hypotension patients due to possible side effects such as fatigue and dizziness[10].
This research compares the efficacy and safety of Metoprolol, Carvedilol, Bisoprolol, and Nebivolol in hospitalized HFrEF and HFpEF patients, measuring NT-proBNP levels, hemodynamic measures, and adverse effects to find the best beta-blocker for HF treatment

## METHODOLOGY

**Study Design:** A prospective observational research study.
**Study Location**: The research was conducted at the Department of Cardiology, Aware Gleangles Hospital in Hyderabad.
**Sample Size:** 100 patients
**Study Duration**: The study was performed over a period of six months.

**Ethical statement: This study was performed only after approval from ethics committee.**
**Statistical Analysis Plan:**
**Statistical Techniques:**
Continuous variables: t test
**Categorical variables:** Chi square or Fisher's exact test
Multivariate analysis to account for confounding variables
Survival analysis for time dependent outcomes

**Inclusion Criteria:**

- Individuals must be 18 years of age or older
- Confirmed and diagnosed as Heart failure
- Currently receiving beta blocker treatment
- Documented ejection fraction
- Hospitalized due to heart failure exacerbation
- Patients willing to provide informed consent
- Patients willing to engage in the study.

**Exclusion Criteria:**

- Contraindications for the use of beta blockers
- Participants unwilling to take part in the study.
- Participants not agreeing to provide consent.

**Primary Endpoints**
**1.** Variation in vital signs from admission to discharge:
Blood pressure
Heart rate
**2. Adverse events occurring during the hospital stay**
**3. Duration of hospital stay**

**Secondary Endpoints**
**1. Variations in:**
NTproBNP levels

**2. Drug interactions**
**Methodology:**

- A study will be carried out to evaluate patients (both male and female) diagnosed with HFpEF and HFrEF.
- Baseline demographic information will be gathered from patient case reports.
- The outcomes of this study will be assessed by monitoring vital signs, laboratory results, and prescribed dosages for HFpEF and HFrEF.

The data obtained will be evaluated and analysed using statistical methods.

**Data Collection Parameters:**
**1. Demographics:**
Age
Gender
Admission/Discharge dates
**2. Clinical Parameters:**
Chief complaint
Past medical history
Vital signs
NYHA classification
**3. Laboratory Data:**
Cardiac markers
2D Echo parameters
Adverse events
**4. Subgroup Analyses:**
Age categories
Gender
Comorbidities
Specific beta blockers

**Resources for Study:**
**Informed Consent Form**: To facilitate the patient's understanding, an informed consent form has been created in Telugu, Hindi, and English.
**Patient Information Page**: patient information document was developed that outlines the study's purpose, potential risks, benefits, alternatives, confidentiality, and contact information for any further questions or concerns.
**Patient collection form:** Patients with or without comorbidities using beta-blockers like bisoprolol, metoprolol, carvedilol, and nebivolol, as well as those diagnosed with either heart failure with reduced ejection fraction (HFrEF) or preserved ejection fraction (HFpEF), were included in the study. The patient collection form gathered demographic information, such as age, gender, NYHA class, NT-proBNP levels, hospitalization duration, symptom improvement, and adverse effects.
**Trial Protocol:** After obtaining informed consent, participants received a brief explanation of the study and signed the consent form.

**Study procedure:**
Under the guidance of the hospital's cardiologist, the study included one hundred patients. Data was collected from hospitalized individuals in the cardiac unit at Gleneagles Aware Hospital and analysed using statistical software, leading to relevant conclusions.

## RESULTS

Throughout the duration of the study, a total of 100 patients were recruited based on the inclusion criteria,

while those who did not meet the exclusion criteria were left out of the study.

**Table 1: Demographics and Baseline Characteristics**

| Parameter | HFpEF (n=50) | HFpEF (n=50) | P value |
|---|---|---|---|
| Age (mean ± SD) | 68 ± 8 years | 62 ± 10 years | p=0.001 |
| Male (%) | 26 (52%) | 34 (68%) | p=0.042 |
| Female (%) | 24 (48%) | 16 (32%) | p=0.042 |
| NYHA Class III/IV (%) | 32 (64%) | 38 (76%) | p=0.134 |
| Hypertension (%) | 39 (78%) | 17 (34%) | p<0.001 |
| Diabetes Mellitus (%) | 30 (60%) | 22 (44%) | p=0.048 |

The demographic information revealed that patients with HFpEF had an average age of 68 ± 8 years, in contrast to HFrEF patients who averaged 62 ± 10 years(p=0.001). The HFpEF group consisted of 52% males ( p=0.042) and 48% females( p=0.042), whereas the HFrEF group had a higher male percentage of 68% and a female percentage of 32%. NYHA Class III/IV classifications were noted in 64% of patients with HFpEF and in 76% of those with HFrEF(p=0.134). Hypertension was notably more common in HFpEF at 78%, compared to 34% in HFrEF(p=<0.001), and diabetes mellitus was present in 60% of HFpEF patients versus 44% of HFrEF patients p=0.048).

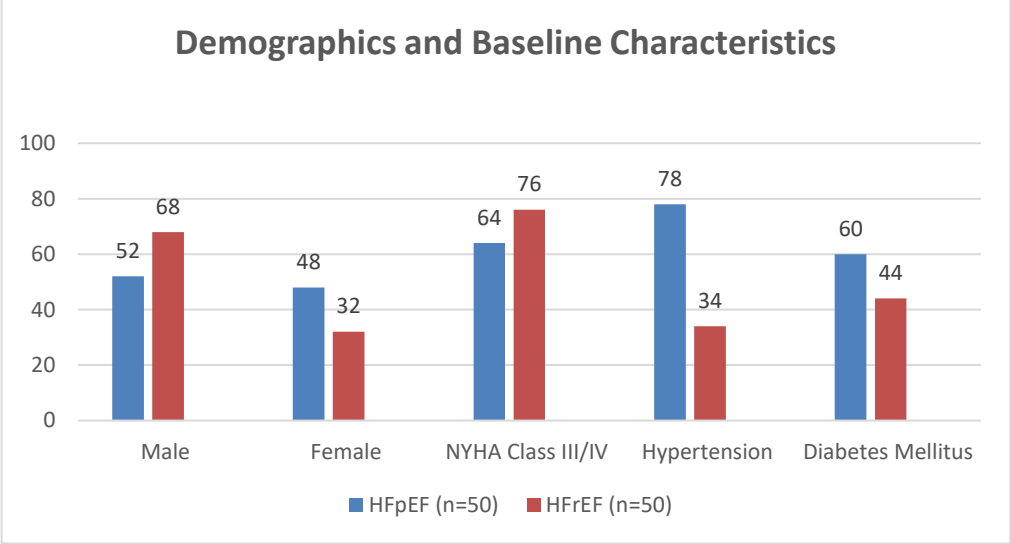


**Figure 1: Demographics and Baseline Characteristics**

**Table 2: Comparison of Beta Blocker Utilization**

| Beta Blocker | HFpEF (n=50) | HFrEF (n=50) | Total (n=100) | P value |
|---|---|---|---|---|
| Bisoprolol | 30(60%) | 35(70%) | 65 (65%) | p=0.157 |
| Metoprolol | 10(20%) | 7.5(15%) | 17.5(17.5%) | p=0.311 |
| Carvedilol | 5(10%) | 4(8%) | 9(9%) | p=0.726 |
| Nebivolol | 5(10%) | 3.5(7%) | 8.5(8.5%) | p=0.569 |

Beta blocker utilization showed that Bisoprolol was prescribed in 60% of HFpEF and 70% of HFrEF patients(p=0.157), Metoprolol in 20% of HFpEF and 15% of HFrEF (p=0.311), Carvedilol in 10%of HFpEF and 8% of HFrEF (p=0.726), and Nebivolol in 10% of HFpEF and 7% of HFrEF (p=0.596), respectively.

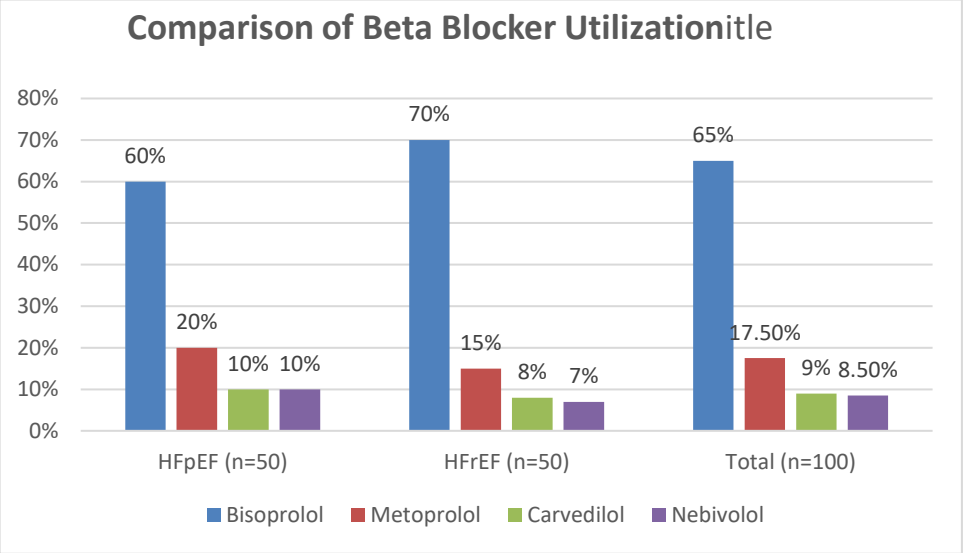


**Figure 2: Comparison of Beta Blocker Utilization**

**Table 3: Safety Outcomes by Beta Blocker**

| Beta Blocker | Bradycardia (%) | Hypotension (%) | Worsened HF Symptoms (%) | Fatigue (%) | Dizziness (%) | P value |
|---|---|---|---|---|---|---|
| Bisoprolol | 6% | 8% | 4% | 10% | 8% | Reference |
| Metoprolol | 10% | 12% | 6% | 14% | 12% | p=0.038 |
| Carvedilol | 12% | 14% | 8% | 18% | 14% | p=0.012 |
| Nebivolol | 8% | 10% | 6% | 12% | 10% | p=0.245 |

Bisoprolol exhibited the lowest rates of side effects, including bradycardia (6%), hypotension (8%), and aggravated HF symptoms (4%), when compared to other beta blockers. Carvedilol, on the other hand, had the highest incidence of fatigue (18%) and dizziness (14%), which may restrict its effectiveness in certain patients. These findings indicate that Bisoprolol presents a more advantageous safety profile, making it especially appropriate for older and comorbid patients with HFpEF who are at greater risk for side effects.

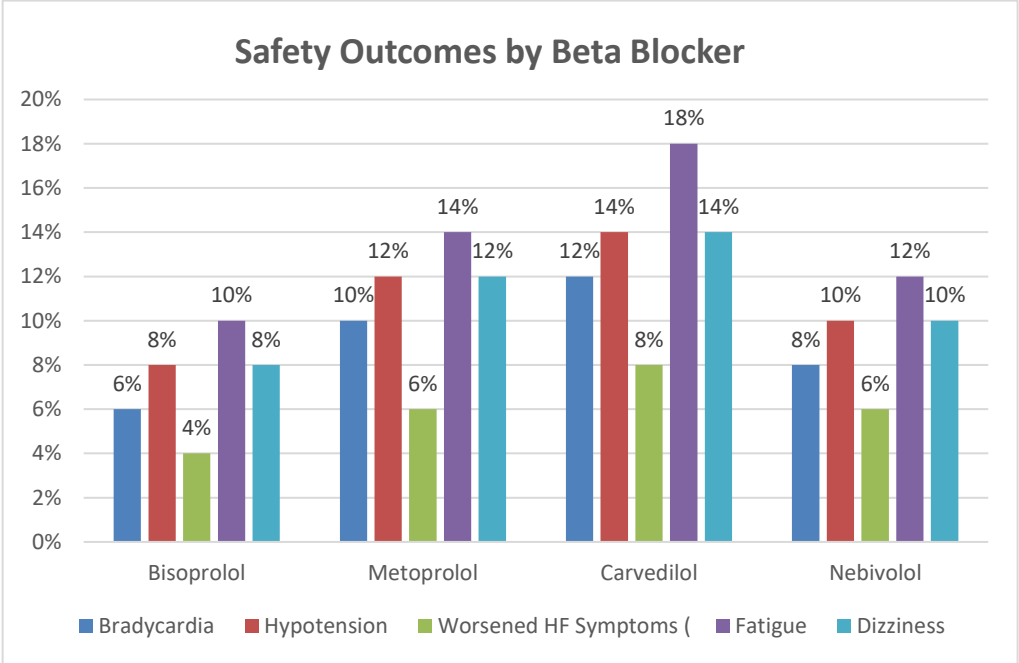


**Figure 3: Safety Outcomes by Beta Blocker**

**Table 4: Efficacy Outcomes by Beta Blocker**

| Beta Blocker | HFpEF Reduction in NTproBNP (%) | HFrEF Reduction in NTproBNP (%) | Improvement in NYHA Class (%) | Length of Stay (days) | P value |
|---|---|---|---|---|---|
| Bisoprolol | 22% | 30% | 52% | 5.6 ± 1.8 | Reference |
| Metoprolol | 18% | 26% | 44% | 6.2 ± 2.1 | p=0.024 |
| Carvedilol | 16% | 24% | 40% | 6.5 ± 2.3 | p=0.008 |
| Nebivolol | 20% | 28% | 48% | 5.8 ± 2.0 | p=0.312 |

In terms of effectiveness, Bisoprolol decreased NTproBNP levels by 22% in HFpEF and by 30% in HFrEF, enhanced NYHA class in 52% of patients, and reduced the average hospital stay to 5.6 ± 1.8 days compared to Metoprolol led to an 18% reduction in NTproBNP in HFpEF and a 26% reduction in HFrEF, improved NYHA class in 44% of cases(p=0.024), and resulted in a hospital stay duration of 6.2 ± 2.1 days. Carvedilol(p=0.008) and Nebivolol (p=0.312)exhibited slightly lower efficacy measures when compared to Bisoprolol.

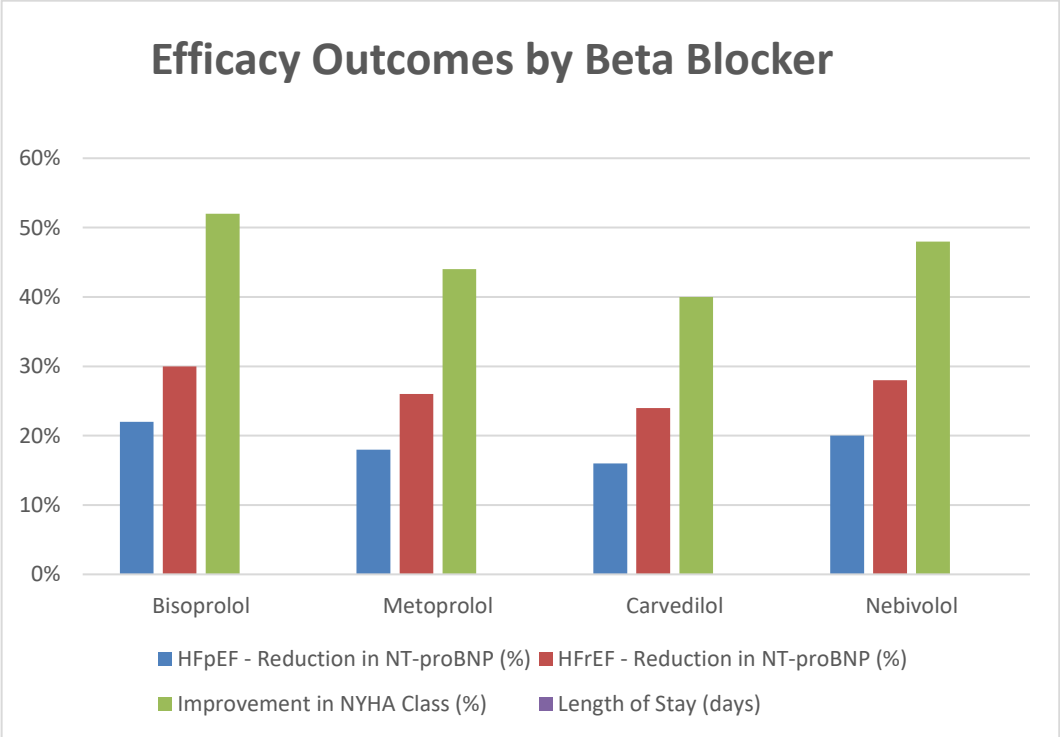


**Figure 4: Efficacy Outcomes by Beta Blocker**

**Table 5: Hospitalization Outcomes**

| Parameter | HFpEF (n=50) | HFrEF (n=50) | Total (n=100) | P value |
|---|---|---|---|---|
| Median ICU Stay (days) | 2.2 days | 1.8 days | 2.0 days | p=0.042 |
| Median Ward Stay (days) | 4.2 days | 4.0 days | 4.1 days | p=0.384 |
| Discharge to Home (%) | 90% | 94% | 92% | p=0.357 |
| Discharge to Rehab (%) | 10% | 6% | 8% | p=0.357 |

Hospitalization results indicated that patients with HFpEF had an average ICU stay of 2.2 days, compared to 1.8 days for those with HFrEF, while the average ward stay was 4.2 days for HFpEF and 4.0 days for HFrEF. Among the patients, 90% of those with HFpEF and 94% of those with HFrEF were discharged to their homes, whereas 10% and 6% were discharged to rehabilitation facilities, respectively. A gender specific breakdown revealed that bradycardia was present in 10% of male patients and 8% of female patients, hypotension was observed in 12% of males and 10% of females, and fatigue occurred in 14% of males and 12% of females.

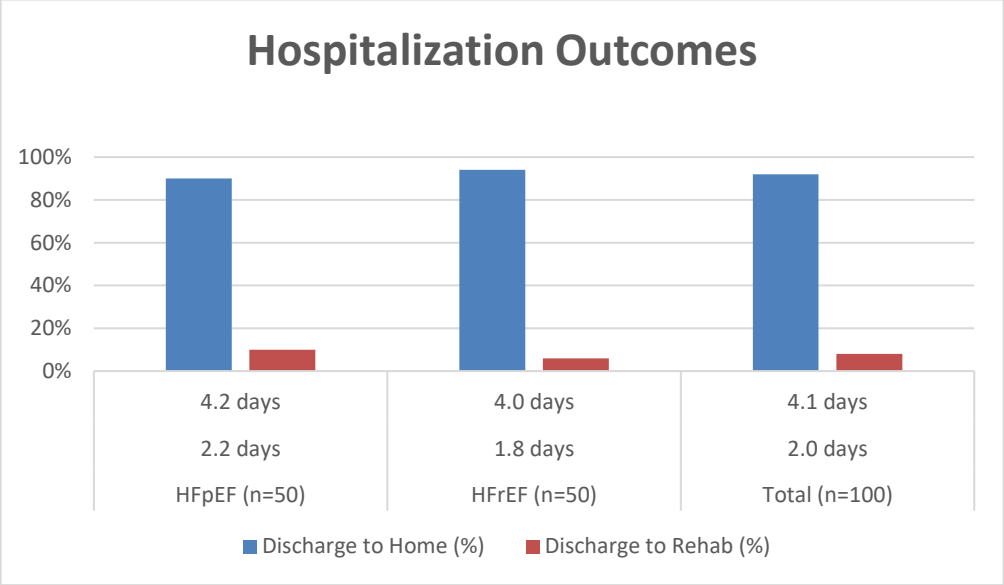


**Figure 5: Hospitalization Outcomes**

**Table 6: Adverse Effects by Gender**

| Adverse Effect | Male (n=60) | Female (n=40) | Total (n=100) |
|---|---|---|---|
| Bradycardia (%) | 10% | 8% | 9% |
| Hypotension (%) | 12% | 10% | 11% |
| Fatigue (%) | 14% | 12% | 13% |
| Dizziness (%) | 10% | 8% | 9% |
| Worsened HF Symptoms (%) | 6% | 4% | 5% |

Regarding adverse effects based on gender, bradycardia was observed in 10% of men and8% of women, hypotension in 12% of men and 10% of women, fatigue in 14% of men and 12% of women, dizziness in 10% of men and 8% of women, and exacerbated HF symptoms in 6% of men and 4% of women.

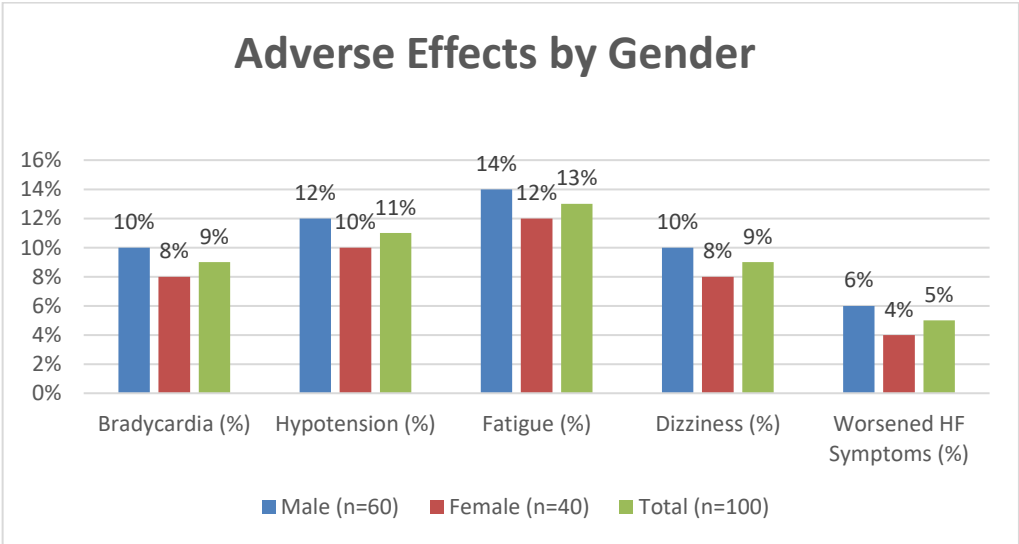


**Figure 6: Adverse Effects by Gender**

**Table 7: Beta Blocker Outcomes in HF Subtypes**

| Parameter | Bisoprolol (HFpEF) | Bisoprolol (HFrEF) | Metoprolol (HFpEF) | Metoprolol (HFrEF) |
|---|---|---|---|---|
| NTproBNP Reduction (%) | 22% | 30% | 18% | 26% |
| Improvement in NYHA Class (%) | 50% | 54% | 40% | 48% |
| Symptom Improvement (%) | 60% | 65% | 50% | 55% |
| Length of Stay (days) | 5.4 ± 1.7 | 5.8 ± 1.9 | 6.0 ± 2.0 | 6.4 ± 2.2 |

In terms of beta blocker effectiveness, Bisoprolol reduced NTproBNP levels by 22% in patients with HFpEF and 30% in those with HFrEF, enhanced NYHA class by 50% and 54%, and resulted in 60% and 65% symptom improvement, with average hospital stays of 5.4 ± 1.7 and 5.8 ± 1.9 days, respectively. Metoprolol decreased NTproBNP levels by 18% in HFpEF and 26% in HFrEF, improved NYHA class by 40% and 48%, and achieved 50% and 55% symptom improvement, with longer hospital stays of 6.0 ± 2.0 and 6.4 ± 2.2 days.

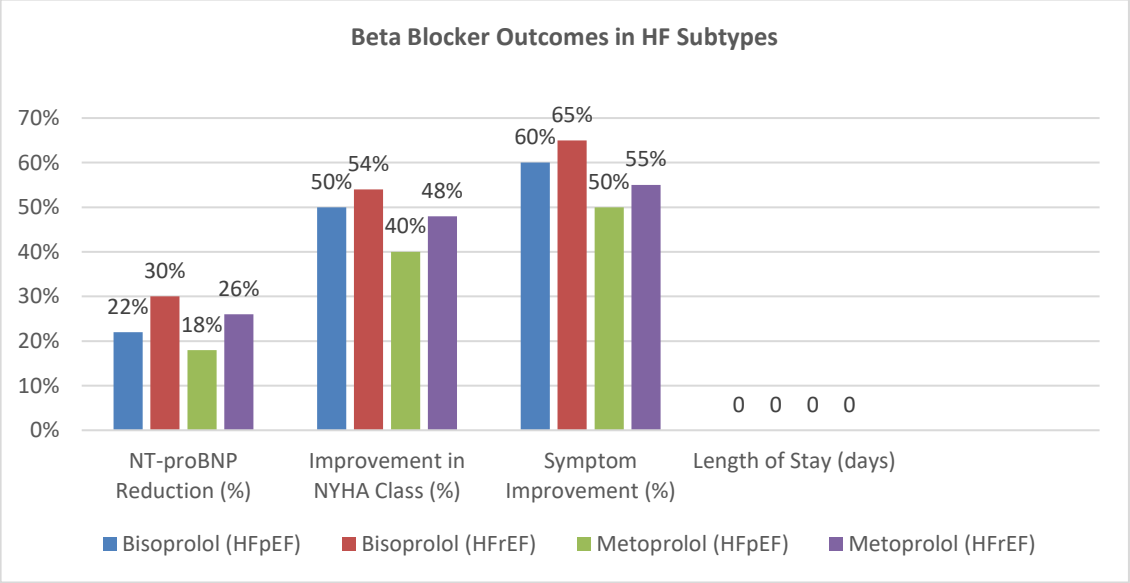


**Figure 7: Adverse Effects by Gender**

## DISCUSSION

Heart failure (HF) is a serious global health concern with various clinical presentations that necessitate specialized treatment strategies[11]. It is typically categorized based on left ventricular ejection fraction into heart failure with preserved ejection fraction and heart failure with reduced ejection fraction[12,13]. While both categories exhibit similar symptoms and often coexist with other health conditions, their underlying pathophysiology differs, requiring tailored approaches to management[14]. Beta-blockers are the cornerstone therapies for HFrEF and have demonstrated efficacy in reducing mortality, hospitalizations, and symptomatology by decreasing neurohormonal activation and improving cardiac efficiency[15]. However, there is limited evidence regarding their effectiveness in HFpEF, and their role in this subset remains uncertain[16].

This study emphasizes the comparative safety and efficacy of bisoprolol, metoprolol, carvedilol, and nebivolol in patients with HFpEF and HFrEF during hospitalization. Among the four beta blockers, bisoprolol emerged as the safest and most effectiveoption for both types of heart failure. The most significant reductions in NTproBNP levels—22% in patients with HFpEF and 30% in those with HFrEF indicate its efficacy[17]. These findings are corroborated by other studies, including CIBISII[18], which highlighted the advantageous effects of bisoprolol in decreasing morbidity and mortality in HFrEF patients. Although there is a scarcity of clinical trials focusing on the effects of bisoprolol in HFpEF, observational studies indicate that it may provide comparable benefits in symptom management and biomarker reduction[19].

The 52% improvement in NYHA functional class observed across both heart failure types underscores the superiority of Bisoprolol, further validating its therapeutic role in managing acute symptom burden. In contrast, metoprolol and carvedilol showed limited effectiveness, resulting in NTproBNP reductions of 18% and 16% in HFpEF, and 26% and 24% in HFrEF, respectively[20,21].

These results align with findings from the MERITHF[22] and CAPRICORN[23] studies, which support their role in enhancing clinical outcomes in HFrEF patients. Nebivolol demonstrated moderate effectiveness as well, achieving a 20% NTproBNP reduction in HFpEF and 28% in HFrEF. The SENIORS study[24] has provided substantial evidence of its benefits for older heart failure patients, suggesting its potential application in a specific patient demographic.

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## CONCLUSION

The study indicates that Bisoprolol demonstrates superior safety and efficacy compared to Metoprolol, Carvedilol, and Nebivolol in patients with both HFpEF and HFrEF. Its clinical significance is underscored by its ability to reduce side effects, improve NYHA class, and significantly decrease NTproBNP levels. These findings emphasize the need for further research to validate these results and refine treatment strategies for managing heart failure.

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