https://doi.org/10.48047/AFJBS.6.16.2024.4238-4243

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

Comparative Efficacy of Beta-Blockers in Heart Failure: A Multicenter Randomized Study

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Volume 6, Issue 16, Dec 2024

Received: 15 June 2024

Accepted: 26 Aug 2024

Published: 09 Dec 2024

doi:10.48047/AFJBS.6.16.2024.4238-4243

Abstract

Background: Heart failure (HF) is a major public health concern with high morbidity and mortality rates worldwide. Beta-blockers are cornerstone therapies for heart failure, particularly in patients with reduced ejection fraction (HFrEF). This study aims to compare the efficacy of three commonly prescribed beta-blockers—carvedilol, metoprolol, and bisoprolol—on clinical outcomes in HF patients.

Objective: To evaluate the comparative efficacy of carvedilol, metoprolol, and bisoprolol in improving left ventricular ejection fraction (LVEF), reducing hospitalizations, and enhancing survival in heart failure patients.

Methods: A multicenter randomized controlled trial was conducted involving 1,200 heart failure patients with HFrEF. Participants were randomly assigned to one of three groups to receive either carvedilol, metoprolol, or bisoprolol for 12 months. Primary outcomes included LVEF improvement, reduction in heart failure-related hospitalizations, and overall mortality. Secondary outcomes assessed adverse events and quality of life (QoL).

Results: Carvedilol demonstrated the most significant improvement in LVEF, compared to metoprolol and bisoprolol. Patients on carvedilol had a 30% reduction in hospitalization rates and a 25% improvement in survival compared to the other two groups. Metoprolol and bisoprolol showed similar benefits, with slightly less efficacy in reducing hospitalizations and improving LVEF. Safety profiles were similar across all three groups, with carvedilol showing a higher incidence of bradycardia and hypotension during dose escalation.

Conclusion: Carvedilol provides superior benefits in improving LVEF, reducing hospitalizations, and enhancing survival in patients with heart failure compared to metoprolol and bisoprolol. While all three beta-blockers are effective, carvedilol should be considered as the preferred first-line therapy in heart failure with reduced ejection fraction.

Keywords: Heart Failure, Beta-Blockers, Carvedilol, Metoprolol, Bisoprolol, Ejection Fraction, Mortality, Hospitalization, Clinical Outcomes.

Introduction

Heart failure (HF) is a progressive condition with high morbidity and mortality rates worldwide. It occurs when the heart is unable to pump blood efficiently, leading to symptoms like shortness of breath, fatigue, and fluid retention[1]. The disease is commonly associated with a reduced ejection fraction (HFrEF), which signifies the heart's decreased ability to contract and pump blood effectively. Effective management of HF is critical, with pharmacologic interventions playing a central role in improving symptoms, preventing disease progression, and improving survival[2-5].

Beta-blockers have been well-established as a cornerstone in the treatment of HFrEF due to their ability to reduce sympathetic nervous system activity, thus preventing further heart damage and improving outcomes. Among the various beta-blockers available, carvedilol, metoprolol, and bisoprolol are frequently used in clinical practice. These medications, however, differ in their pharmacological properties, including their beta-receptor selectivity, additional vasodilatory effects, and impact on mortality and morbidity in heart failure patients[6-10].

Carvedilol, a non-selective beta-blocker with alpha-1 antagonist properties, has demonstrated substantial benefits in terms of improving left ventricular ejection fraction (LVEF), reducing hospitalization rates, and improving long-term survival. The results of the COPERNICUS study (1999) and subsequent trials have established carvedilol as a highly effective agent in the management of heart failure. However, it remains important to explore and compare its efficacy against other beta-blockers, such as metoprolol, a selective beta-1 blocker, and bisoprolol, another beta-1 selective agent.

The aim of this study is to evaluate and compare the clinical efficacy of carvedilol, metoprolol, and bisoprolol in improving clinical outcomes in patients with HFrEF. Specifically, we seek to assess the impact of these beta-blockers on left ventricular ejection fraction, hospitalization rates, mortality, and adverse events in a multicenter randomized controlled trial.

Methods

A multicenter, randomized, controlled trial was designed at Cardiology, Sahiwal Institute of Cardiology, Sahiwal, to compare the efficacy of carvedilol, metoprolol, and bisoprolol in patients with heart failure and reduced ejection fraction. The trial enrolled 1,200 patients from 10 cardiology centers across the country. Inclusion criteria included adults aged 45-80 years with a diagnosis of HFrEF (LVEF < 40%) and symptomatic heart failure (NYHA class II-IV). Exclusion

criteria included contraindications to beta-blocker therapy, recent myocardial infarction, or significant comorbid conditions such as advanced renal or liver disease.

Patients were randomly assigned to one of three treatment groups: carvedilol, metoprolol, or bisoprolol. All participants received standard heart failure therapy, including angiotensin-converting enzyme inhibitors (ACE inhibitors), diuretics, and/or aldosterone antagonists. Beta-blockers were titrated to target doses as per current clinical guidelines.

The primary outcomes of the study were changes in LVEF, heart failure-related hospitalizations, and overall mortality. Secondary outcomes included adverse events, changes in quality of life (QoL), and 6-minute walk distance. Data were analyzed using intention-to-treat methodology, and statistical significance was determined using a p-value of <0.05.

Results

The baseline characteristics of patients were comparable across all three groups, with no significant differences in age, sex, and comorbid conditions. At the 12-month follow-up, patients in the carvedilol group showed a 25% improvement in LVEF compared to baseline, significantly greater than the 15% improvement seen in the metoprolol group ($p = 0.02$) and the 18% improvement seen in the bisoprolol group ($p = 0.05$).

Regarding hospitalizations, patients on carvedilol experienced a 30% reduction in hospital admissions due to heart failure exacerbations, significantly higher than the 20% reduction in the metoprolol group ($p = 0.03$) and the 15% reduction in the bisoprolol group ($p = 0.04$). Mortality rates at 12 months were significantly lower in the carvedilol group (12%) compared to the metoprolol (17%) and bisoprolol groups (18%) ($p = 0.01$).

Adverse events were more frequently reported in the carvedilol group, particularly bradycardia and hypotension, though these events were generally manageable with dose adjustment. There were no significant differences in adverse events between the metoprolol and bisoprolol groups.

Discussion

The results of this multicenter randomized trial suggest that carvedilol provides superior benefits in patients with heart failure and reduced ejection fraction when compared to metoprolol and bisoprolol. Carvedilol significantly improved left ventricular ejection fraction, reduced

hospitalizations, and decreased mortality rates more effectively than both metoprolol and bisoprolol. These findings are consistent with previous studies, including the COPERNICUS and CIBIS-II trials, which demonstrated that carvedilol improves clinical outcomes in heart failure patients[11-14].

Carvedilol's additional alpha-blocking activity may contribute to its superior clinical efficacy by improving afterload reduction, enhancing myocardial perfusion, and improving diastolic function. These effects likely explain why carvedilol outperforms metoprolol and bisoprolol in improving LVEF and reducing hospitalization rates[15-18].

Metoprolol and bisoprolol also demonstrated clinical efficacy, improving LVEF and reducing hospitalizations, but to a lesser extent than carvedilol. Both of these beta-blockers are highly effective, particularly in reducing heart rate and myocardial oxygen demand, which are crucial mechanisms in the management of heart failure. However, they lack the additional vasodilatory effects that carvedilol provides[19-20].

Safety profiles were similar across all groups, with carvedilol being associated with a slightly higher incidence of bradycardia and hypotension, particularly during dose titration. This is consistent with the findings of the Carvedilol Heart Failure Study Group and other studies, which report that carvedilol's adverse events are manageable with proper monitoring and dose adjustments.

This study underscores the importance of individualized treatment in heart failure. While carvedilol appears to be the most effective beta-blocker for improving outcomes in HFrEF, the choice of beta-blocker should be based on patient-specific factors, including comorbid conditions, tolerability, and potential side effects.

Conclusion

Carvedilol provides superior clinical benefits in patients with heart failure and reduced ejection fraction compared to metoprolol and bisoprolol. It is associated with a significant improvement in left ventricular ejection fraction, reduced hospitalizations, and lower mortality rates. While metoprolol and bisoprolol are also effective, carvedilol's additional alpha-blocking activity makes it the preferred choice for most heart failure patients. However, patient-specific factors must guide treatment decisions to ensure the best outcomes.

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