Original Article

Comparative Effectiveness of Metoprolol on Clinical Outcomes in Stemi Patients with Midline Versus Preserved Ejection Fraction: A Retrospective Cohort Study

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ABSTRACT

Background: The use of beta-blockers like metoprolol is essential in managing ST-elevation myocardial infarction (STEMI) by reducing myocardial oxygen demand and preventing adverse cardiovascular events. However, the effectiveness of metoprolol may vary depending on the patient's ejection fraction (EF), particularly between midline EF (41-49%) and preserved EF (≥50%). While previous studies indicate that lower EF may increase the risk of complications, the comparative outcomes between midline and preserved EF in beta-blocker therapy remain underexplored. This study addresses this gap by analysing the clinical outcomes of STEMI patients treated with metoprolol, focusing on differences between midline and preserved EF categories.

Methods: A retrospective cohort study was conducted on 103 STEMI patients at Kumaran Medical Centre, Coimbatore, using data from cases diagnosed between 2019 and 2021, with a minimum follow-up period of three years. Patients were categorized into midline EF (n=52) and preserved EF groups (n=51). Outcomes of interest included reinfarction, stroke, heart failure, hypotension, and bradycardia. Statistical analyses were performed using Excel, employing chi-square tests to evaluate associations between EF categories and outcomes, and odds ratios (ORs) to assess the relative risk of adverse events in the midline EF group compared to the preserved EF group.

Results: The study population predominantly consisted of older adults (≥56 years) and was largely male (76.7%), with an average age of 63.2 ± 7.4 years. Statistical analysis revealed significant differences in treatment outcomes for midline vs preserved EF groups, particularly for heart failure (P=0.03) and hypotension (P=0.04). ORs indicated increased risks of heart failure (OR=2.5), reinfarction (OR=1.6), stroke (OR=1.7), hypotension (OR=3.0), and bradycardia (OR=2.1) in midline EF patients compared to preserved EF patients.

Conclusion: Patients with midline EF post-STEMI are at higher risk for adverse outcomes, especially heart failure and hypotension, when treated with metoprolol. These findings underscore the importance of tailored therapeutic strategies in managing STEMI patients based on EF category.

Keywords: ST Elevation Myocardial Infarction, Metoprolol, Ejection Fraction, Stroke, Heart failure, Myocardial Infarction, Adverse Drug Reaction.

INTRODUCTION

ST-Elevation Myocardial Infarction (STEMI) is a critical form of acute myocardial infarction characterized by ST-segment elevation in two or more contiguous leads on an electrocardiogram (ECG), indicating a complete blockage in a coronary artery. This condition results in the death of heart muscle due to a lack of blood flow.[1] As a medical emergency, prompt reperfusion therapy is essential for restoring blood flow, reducing myocardial damage, and improving survival rates.[2] According to the World Health Organization (WHO), ischemic heart disease, including myocardial infarction, is a leading cause of global mortality, accounting for approximately 17.9 million deaths annually.[3] In the United States, despite recent declines in STEMI incidence due to improved preventive measures, it remains a significant healthcare burden, with the American Heart Association (AHA) estimating around 800,000 heart attacks each year, of which 30% are STEMI cases.[4] The economic impact of STEMI is considerable, encompassing both direct and indirect medical costs.[5] Among the treatment approaches, metoprolol, a beta-blocker, stands out as one of the most effective options. Studies have shown that early administration of metoprolol can reduce infarct size, preserve heart function, and lower the risk of adverse cardiovascular events, making it an essential therapy in STEMI management.[6]

Pathophysiology[6]

STEMI arises from the complete occlusion of a coronary artery, typically due to a thrombus forming over a ruptured atherosclerotic plaque. Atherosclerosis involves the accumulation of fatty deposits and cholesterol within arterial walls, leading to plaque formation. The rupture of this plaque triggers the formation of a clot that can rapidly occlude the artery. This blockage prevents oxygen-rich blood from reaching a segment of the myocardium, leading to myocardial ischemia and subsequent cell death (necrosis) if not treated promptly. The extent of myocardial damage is directly related to the duration of occlusion and the size of the affected area.

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Ejection fraction[7]

Ejection fraction (EF) is a key measurement used to assess the heart's pumping efficiency, specifically the percentage of blood that is ejected from the left ventricle with each contraction of the heart. It is an important indicator of cardiac function, providing insight into how well the heart is able to circulate blood throughout the body.

EF (%) = (SV/EDV) ×100

- **SV (Stroke Volume)**: This is the amount of blood pumped out of the left ventricle with each heartbeat. It represents the difference between the volume of blood in the ventricle at the end of diastole (just before contraction) and the volume remaining at the end of systole (after contraction).
- **EDV (End-Diastolic Volume)**: This is the total volume of blood present in the left ventricle at the end of diastole, just before the heart contracts. It reflects the maximum volume of blood the ventricle can hold before it pumps blood into the aorta.

Types of Ejection Fraction

1. **Reduced EF:** Less than 40% - ineffective contraction and lower oxygen delivery.[8]
2. **Midline EF:** Between 40% and 49% - characteristics of both reduced and preserved EF, with variable prognosis.[8]
3. **Preserved EF:** 50% or higher - heart contracts normally but has diastolic filling issues.[9,10]

Beta Blockers

Beta-blockers (β-blockers) are a class of medications commonly used to manage cardiovascular conditions by blocking the action of epinephrine and norepinephrine on β-adrenergic receptors, predominantly β1 receptors in the heart. This action reduces heart rate, myocardial contractility, and cardiac output, which lowers blood pressure and decreases myocardial oxygen demand.[11] STEMI patients treated with metoprolol, a beta-blocker, the use of β-blockers is particularly significant for patients with heart failure, arrhythmias, or reduced ejection fraction (EF). Studies have shown that β-blockers improve survival and reduce the risk of recurrent myocardial infarction by attenuating the harmful effects of sympathetic nervous system activation during acute coronary events.[12]

Classification of Beta-blockers

1. **Non-selective beta-blockers:** These blocks both β1 and β2 receptors, affecting both cardiac and bronchial tissues. **Propranolol and carvedilol** are examples of non-selective beta-blockers.[13] These are typically avoided in patients with respiratory conditions such as asthma due to their broncho constrictive effects.
2. **Cardio selective beta-blockers (β1-selective):** These primarily block β1 receptors in the heart, minimizing respiratory side effects. Common cardio selective beta-blockers include **metoprolol and bisoprolol** mar.[14] These are the preferred choice in patients with comorbid respiratory conditions like asthma or COPD.[8] Cardio selective beta-blockers have shown improved outcomes in heart failure patients.
3. **Beta-blockers with intrinsic sympathomimetic activity (ISA)**: Beta-blockers such as **pindolol and acebutolol**, which have intrinsic sympathomimetic activity, partially activate beta receptors while blocking stronger effects of catecholamines. These are less effective at reducing heart rate and are avoided in patients with heart failure or after myocardial infarction.[15]
4. **Beta-blockers with alpha-blocking properties:** Some beta-blockers, like **carvedilol and labetalol**, also block alpha receptors, leading to vasodilation alongside beta-blockade. This makes them useful in treating hypertension and heart failure.[16]
5. **Beta-blockers with membrane-stabilizing activity:** Beta-blockers such as **propranolol** exhibit local anaesthetic effects by stabilizing cell membranes, though this property is less clinically significant. Membrane-stabilizing activity is mainly noted in high doses.[17]

Mechanism of Action of Metoprolol

Metoprolol is a selective beta-1 adrenergic blocker primarily targeting beta-1 receptors in the heart. Its key actions include:

- **Reduction in Heart Rate:** Metoprolol blocks beta-1 receptors, decreasing heart rate and thereby reducing myocardial oxygen demand. This is particularly beneficial for conditions like ischemic heart disease and myocardial infarction.[16]
- **Decrease in Myocardial Contractility:** It lowers the force of heart muscle contractions, reducing cardiac workload and oxygen consumption.[16]
- **Lowering Blood Pressure:** Metoprolol decreases blood pressure by reducing cardiac output and inhibiting renin release from the kidneys, contributing to its antihypertensive effects.[18]
- **Anti-arrhythmic Effects:** By stabilizing cardiac electrical activity and decreasing sympathetic nervous system activity, metoprolol helps prevent arrhythmias, making it useful in post-myocardial infarction care.[18]

Adverse effects

Common Adverse Effects[19]

1. **Fatigue**: Patients often report feeling unusually tired or fatigued.

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2. **Dizziness**: Light-headedness, especially when standing up quickly, may occur due to its blood pressure-lowering effects.
3. **Bradycardia**: A decrease in heart rate can lead to symptoms like fatigue and dizziness.
4. **Hypotension**: Reduced blood pressure can cause light-headedness and fainting.

Serious Adverse Effects

- **Asthma Exacerbation**: While metoprolol is cardio selective, it can still exacerbate bronchospasm in susceptible individuals.[20]
- **Hypoglycemia**: Metoprolol can mask the symptoms of hypoglycemia in diabetic patients.[19]

Contraindications

1. **Asthma:** Selective for beta-1 receptors, risk of bronchospasm.[21]
2. **Chronic Bradycardia and Hypotension:** These conditions can be exacerbated.[22]

Monitoring

1. **Heart Rate and Blood Pressure:** Regular checks are needed to prevent excessive bradycardia and hypotension.[23]
2. **QTc Interval:** Important for patients on beta-blockers affecting the QT interval.[24]

Despite the established benefits of metoprolol post-stemi, their differential effects based on ejection fraction (EF) categories remain under-explored. specifically, the comparative effectiveness in patients with preserved EF (≥50%) versus midline EF (40-49%) is not well-documented.[25] Understanding these differences is crucial for optimizing treatment strategies.[26] This study aims to provide insights into the efficacy of metoprolol in these subgroups, guiding clinical decision-making and improving patient outcomes. This study seeks to compare the effects of metoprolol in STEMI patients with preserved and midline ejection fractions, focusing on outcomes such as reinfarction, stroke, heart failure, and the incidence of adverse events like bradycardia and hypotension over a three-year follow-up period. It is hypothesized that patients with preserved EF will exhibit better clinical outcomes, with fewer adverse events, compared to those with midline EF. [27] Additionally, it is anticipated that the midline EF group will experience a higher incidence of bradycardia and hypotension due to increased cardiovascular strain.

MATERIALS AND METHODS

A retrospective cohort study analysed STEMI patients treated with metoprolol, categorized by midline (ejection fraction [EF] 41-49%) or preserved (EF ≥50%) ejection fractions.[27] A total of 186 patients diagnosed with STEMI between 2019 and 2021 were initially considered, with inclusion criteria comprising those with documented metoprolol treatment during hospitalization or follow-up, and at least three years of follow-up data available.[28] The study ultimately included 103 patients, with 52 in the midline EF group and 51 in the preserved EF group, based on the defined inclusion and exclusion criteria. Exclusion criteria included patients unable to receive metoprolol due to contraindications (e.g., severe asthma, bradycardia) and those with incomplete records. Statistical analyses were performed using Microsoft Excel, employing descriptive statistics for demographic and clinical variables and inferential statistics, including chi-square tests and odds ratios, to evaluate associations between EF categories and clinical outcomes, The p-value <0.05 was considered statistically significant.[29] Data were collected from electronic medical records at Kumaran Medical Centre, Coimbatore.[30] Ethical approval for the study was obtained from the Institutional Ethical Committee (IEC) prior to data collection.[31] The materials included the following variables: The variables included demographic data (age, gender, comorbid conditions such as hypertension, diabetes mellitus, Hyperlipidemia, obesity, and lifestyle factors), vitals (blood pressure, heart rate, respiratory rate, and SpO2 levels), clinical data (STEMI characteristics, EF measurements obtained through echocardiography, details of beta-blocker therapy, and concurrent medications), and outcomes (reinfarction, stroke, heart failure, bradycardia, and hypotension) with a minimum follow-up period of three years.

RESULTS AND DISCUSSION

In the present study, both descriptive and inferential statistical analyses were performed to comprehensively evaluate the data and test the hypotheses.[29] Descriptive statistics were employed to summarize the key characteristics of the dataset, providing insights into the central tendencies and variability of the variables under investigation.[32] To further explore the relationships between variables and assess the significance of the findings, statistical tests were conducted. These tests included [chi-square test & odds ratio], which were selected based on the data distribution and the objectives of the study.[33] The results of these analyses are aimed at determining whether observed patterns are statistically significant and generalizable beyond the study sample.

Cohort Demographics: Age and Gender

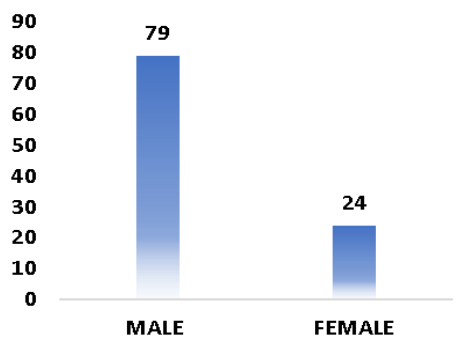

Figure 1: Distribution of Gender

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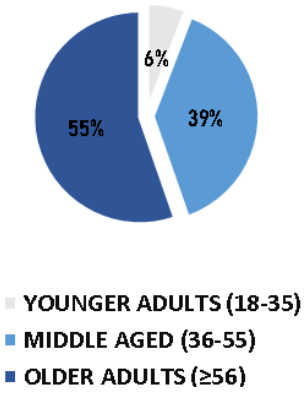

Figure 2: Distribution of Age

The study cohort consists of 103 patients, predominantly male (79 patients, 76.7%) compared to female (24 patients, 23.3%). The age distribution primarily includes middle-aged (36-55 years) and older adults (≥56 years), with fewer younger adults (18-35 years). As shown in **Figure 1&2,** the study's male and older demographic may influence the higher incidence of adverse events.

Table 1: Demographic and Clinical Characteristics

Variable	Preserved EF (51)	Midline EF (52)
Age (years)	Mean (SD): 62 (10)	Mean (SD): 65 (14)
BMI	Median (IQR): 27.2 (17.1-37.2)	Median (IQR): 28.2(17.5-37)
Male (%)	80%	71%
Hypertension (%)	41%	60%
Diabetes (%)	16%	25%
Hyperlipidaemia (%)	20%	29%

In our study, patients with midline ejection fraction (EF) had a higher mean age (65 years vs. 62 years) and slightly higher median BMI (28.2 vs. 27.2) compared to those with preserved EF. The proportion of males was higher in the preserved EF group (80%) than in the midline EF group (71%). Additionally, hypertension and diabetes were more prevalent in the midline EF group (60% and 25%, respectively) compared to the preserved EF group (41% and 16%). Hyperlipidaemia was also more common in the midline EF group (29% vs. 20%). These differences in baseline characteristics may influence the clinical outcomes observed in the study, as shown in Table 1.

Primary outcomes

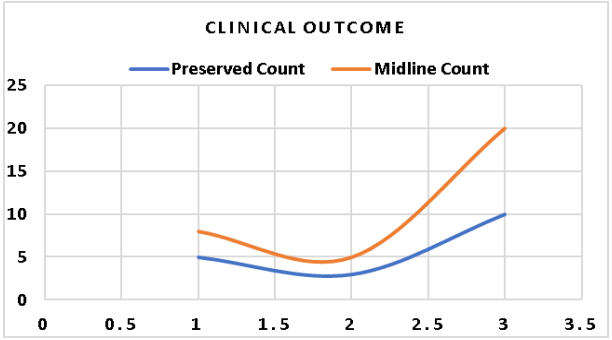

Figure 3: Primary Outcomes

Patients with midline ejection fraction exhibited a higher incidence of adverse events compared to those with preserved ejection fraction. Specifically, reinfarction occurred in 8 patients with midline EF compared to 5 with preserved EF, while stroke was observed in 5 midline EF patients versus 3 in the preserved EF group. Additionally, heart failure was more prevalent in the midline EF cohort, with 20 cases compared to 10 in the preserved EF group. Overall, midline EF was associated with significantly increased rates of reinfarction, stroke, and heart failure, as illustrated in Figure 3.

Secondary outcomes

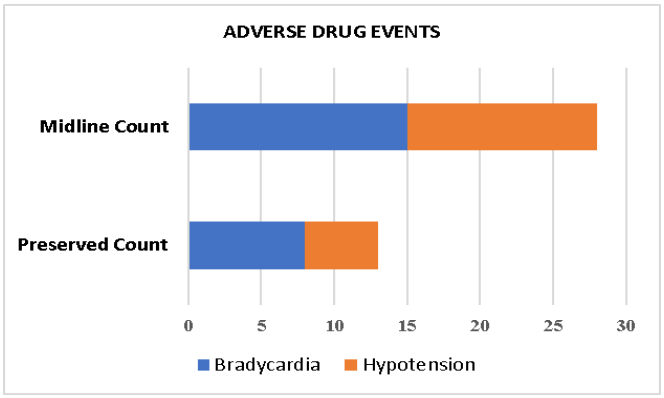

Figure 4: Secondary Outcomes

Bradycardia was observed in 15 cases within the midline ejection fraction (EF) group, compared to 8 cases in the preserved EF group. Similarly, hypotension was recorded in 13 cases among the midline EF patients, whereas only 5 cases were noted in the preserved EF group. These findings indicate that midline ejection fraction is associated with a higher incidence of both cardiovascular events and adverse drug reactions compared to preserved ejection fraction, as illustrated in Figure 4.

Chi – square test

Chi-square tests were employed to evaluate categorical variables, with p-values indicating statistical significance. To quantify the associations between treatment outcomes and ejection fraction categories, odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Standard errors (SEs) were used to provide precision estimates for effect sizes. A p-value of less than 0.05 was deemed statistically significant.

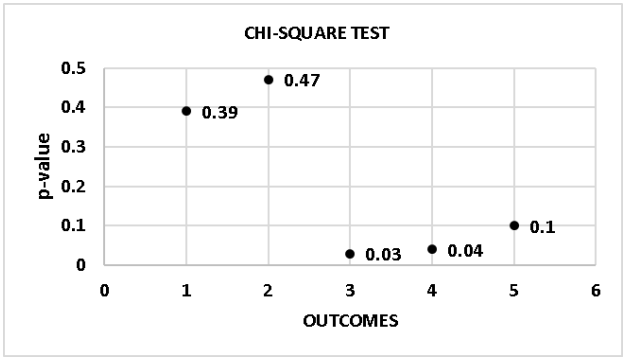

Figure 5: CHI- Square Test on Outcomes

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The analysis reveals that heart failure (p=0.03) and hypotension (p=0.04) are statistically significant, leading to the rejection of the null hypothesis for these outcomes. Conversely, reinfarction (p=0.39), stroke (p=0.47), and bradycardia (p=0.1) did not reach statistical significance. Additionally, the overall p-value of 0.018 indicates significant differences in adverse event rates between ejection fraction groups. This information is visually represented in the illustration (Figure 5), which highlights the outcomes and their p-values.

Odds ratio (risk ratio)

Odds ratios (ORs) were calculated to assess the relative likelihood of adverse outcomes based on ejection fraction status. These ratios help quantify the impact of ejection fraction on patient outcomes, highlighting significant differences between groups.

Table 2: Odds Ratio Analysis

OUTCOMES	ODDS RATIO
HEART FAILURE	**2.5**
REINFARCTION	**1.6**
STROKE	**1.7**
HYPOTENSION	**3**
BRADYCARDIA	**2.1**
TOTAL	**2.063763**

Patients with midline ejection fraction face a significantly higher risk of adverse outcomes compared to those with preserved ejection fraction. As indicated in Table 2, the odds ratios demonstrate that midline patients are 3 times more likely to experience hypotension, 2.5 times more likely to develop heart failure, 2.1 times more likely to suffer from bradycardia, 1.7 times more likely to have a stroke, and 1.6 times more likely to experience reinfarction. Overall, the total odds ratio of 2.06 suggests that patients with midline ejection fraction are approximately twice as likely to encounter these adverse events compared to those with preserved ejection fraction.

Interpretation of results

The study examined the comparative effectiveness of metoprolol in patients with ST-elevation myocardial infarction (STEMI) who had either midline ejection fraction (41-49%) or preserved ejection fraction (≥50%). The results offer significant insights into the cardiovascular risk profiles and outcomes for these two groups.

a) Descriptive Analysis

The study analysed 103 STEMI patients to compare the effectiveness of metoprolol based on ejection fraction (EF) categories. Patients with midline EF (41-49%) had a higher mean age (65 years) and median BMI (28.2) compared to those with preserved EF (≥50%), who had a mean age of 62 years and median BMI of 27.2.[35,36] Gender distribution favoured males in the preserved EF group (80%) versus the midline EF group (71%).[34]

Comorbidities such as hypertension (60% vs. 41%) and diabetes (25% vs. 16%) were more prevalent in the midline EF group, along with Hyperlipidemia (29% vs. 20%).[37] These differences, illustrated in Table 1, may influence clinical outcomes. Clinical events showed that midline EF patients had higher rates of reinfarction (8 vs. 5), strokes (5 vs. 3), and heart failure (20 vs. 10) compared to the preserved EF group, as shown in Figure 3. Additionally, adverse drug reactions were more common in the midline EF group, with 15 cases of bradycardia and 13 cases of hypotension compared to 8 and 5 cases in the preserved EF group, respectively, illustrated in Table 3. Overall, these findings indicate that midline EF is associated with higher rates of adverse outcomes, highlighting the importance of considering EF categories in the efficacy and safety of metoprolol for STEMI patients.[38]

b) Inferential Analysis

- Chi-Square Analysis: Significant differences were observed in the incidence of heart failure (p = 0.03) and hypotension (p = 0.04). The overall p-value of 0.01817 indicates statistically significant differences in adverse outcomes based on ejection fraction status.
- Odds Ratios: Patients with midline ejection fraction exhibited increased risks for various adverse outcomes, with odds ratios (ORs) calculated as follows: 2.5 for heart failure, 1.6 for reinfarction, 1.7 for stroke, 3.0 for hypotension, and 2.1 for bradycardia. These findings reflect a generally elevated risk of complications associated with midline ejection fraction.

Limitations[39,40]

- The sample size may limit generalizability to broader populations.
- Findings are derived from a single medical centre, which may affect applicability to other settings.
- The absence of power analysis raises concerns about the adequacy of the sample size.
- The use of Excel for statistical analysis may limit the robustness of the findings.
- Future research with larger, multi-centre cohorts is needed to validate these results.

CONCLUSION

The study reveals that STEMI patients with midline ejection fraction (EF) face a significantly higher risk of adverse outcomes, including heart failure, hypotension, and bradycardia, compared to those with preserved EF. The odds ratios suggest that midline EF patients are about twice as likely to experience these complications, underscoring the need for vigilant monitoring and tailored

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treatment. These findings highlight that a one-size-fits-all approach may not be adequate and call for individualized care strategies to optimize outcomes in this high-risk population.

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