Indian Journal of Pharmacy and Pharmacology 2023;10(4):281–287

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Indian Journal of Pharmacy and Pharmacology

Journal homepage: https://www.ijpp.org.in/

Original Research Article

Efficacy of Metoprolol and Apixaban in the treatment of cardiovascular diseases: A meta-analysis

Prajila Mavila[1]*, **Mohammad Chand Jamali**[2]

[1]*Al Shaheen Paramedical College and Hospital, Masrakh, Saran, Bihar, India*
[2]*Faculty of Health and Medical Sciences, Liwa College, Al Ain, Abu Dhabi, United Arab Emirates*

ARTICLE INFO

Article history:
Received 05-12-2023
Accepted 19-12-2023
Available online 22-01-2024

Keywords:
Apixaban
Metoprolol
Cardiovascular disease
Meta-analysis

ABSTRACT

Background: Cardiovascular diseases (CVDs) are the major cause of health problems and death worldwide.
Objective: To review the efficacy of Metoprolol and Apixaban in the treatment of cardiovascular diseases by meta-analysis studies.
Materials and Methods: Various databases like PubMed, SciELO, Scopus, Google Scholar, and ResearchGate were used to collect the related studies that were published in English during the years 1980-2013. Only Random Clinical Trials (RCT) were included in this analysis. Risk bias assessment was according to the Cochrane Handbook for Systemic Reviews of the Interventions 6.4. Meta-analysis was done with the help of RevMan 5.4 software.
Results: A total of 10 (one study with different drug concentrations) related articles with 33312 patients were selected for this meta-analysis. In the Metoprolol-treated observation group of patients, the rate of cardiovascular mortality/morbidity [M.H=0.80,95%CI=0.67-0.95, Z=2.5, and P=0.01] was lower and in Apixaban-treated patients [M.H=0.32,95%CI=0.08-1.19, Z=1.7 and P=0.09] the rate of cardiovascular mortality/morbidity were higher and the difference was noted.
Conclusions: It's clear that Apixaban and Metoprolol have a great role in treating cardiovascular diseases. The authors however acknowledge the presence of publication bias and limitations stemming from small sample sizes in some studies, demonstrating a critical and unbiased approach to analysis. Furthermore, it wisely calls for future research endeavors with larger sample sizes, contributing to the ongoing enhancement of treatments for cardiovascular diseases. This balanced and forward-looking analysis consolidates the importance of pharmaceutical interventions in managing cardiovascular diseases.

1. Introduction

In the modern era, cardiovascular disease (CVD) stand out as a prominent global cause of both mortality and morbidity. 20.5 million people died from cardiovascular diseases.[1] Also, the rate of CVD death has increased gradually over the years.

CVD encompasses a range of illnesses affecting the cardiovascular system and is influenced by various factors, including age, gender, smoking, lifestyle choices, and hereditary predispositions.[2] Among the array of treatments, cardiovascular drugs take center stage as the most widely used therapies for CVD.[3]

Tailored to specific types of cardiovascular diseases, various drugs and therapies have been established to effectively reduce the risks associated with CVD.[4] Notably, two vital cardiovascular drugs are Metoprolol and

* *Corresponding author*.
E-mail address: prajilamavila@gmail.com (P. Mavila).

https://doi.org/10.18231/j.ijpp.2023.048

Apixaban, classified as a beta-blocker and an anticoagulant, respectively. Metoprolol, a beta-blocker, exerts its effects by regulating heart rate and mitigating the impact of blood pressure-controlling hormones, effectively reducing high blood pressure.[5] Its action is specific to cardiac cells, inhibiting beta 1-adrenergic receptors and leading to reduced cardiac output through negative chronotropic and inotropic effects.[6]

In contrast, Apixaban operates as a direct oral anticoagulant by inhibiting factor Xa, offering significant stroke prevention benefits.[7] Its inhibition of both free and clot-bound factor Xa leads to anticoagulation, making it a valuable tool in managing venous and arterial thromboembolism.[8]

While numerous studies have explored the individual efficacy of Metoprolol and Apixaban, comparative research has been relatively limited. To address this gap, a meta-analysis was conducted, focusing on studies involving patients treated with either Metoprolol or Apixaban, specifically examining cardiovascular mortality and morbidity. The findings from this study hold the potential to assist healthcare practitioners in making informed decisions when selecting appropriate treatments for CVD cases that can lead to fatal outcomes. It was a meta-analysis of the efficacy of Metoprolol and Apixaban in treating CVD.

2. Materials and Methods

2.1. Literature collection

This study was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)guidelines.[9] Relevant literature was retrieved from different databases by using CVD, cardiovascular drugs, Metoprolol, Apixaban, and cardiovascular mortality/morbidity as the main subject terms. PubMed, Google Scholar, Scopus, ResearchGate, Science Direct, SciELO, etc databases were mainly used for the literature retrieval.

2.2. Inclusion and exclusion criteria

Some inclusion and exclusion criteria were followed to filter the relevant articles. Inclusion criteria include (a) Only Random Controlled Trials (RCT), and adult patients were considered for this analysis. (b) Original research report of randomized design of different groups. (c) Articles which were published in English. (d) Articles which were published from 1980 to 2013.

The exclusion criteria include (a) Studies with less than 100 patients (b) Abstract, uncompleted data, reviews, summary of treatment, and comparative studies.

2.3. Data extraction

A self-developed extraction table was used for the data extraction. Each data was cross-checked after extraction. The data extracted from the selected articles include,

1. Which cardiovascular drug used
2. Baseline characters
3. Intervention measures and control measures
4. Outcome
5. Treatment effect rate, total mortality/morbidity of Metoprolol and Apixaban treated patients.
6. Treatment duration and drug concentration.

2.4. Literature bias assessment

A comprehensive literature bias assessment was conducted to identify various biases present in the selected studies. The selection criteria encompassed a range of biases, including selection bias, implementation bias, measurement bias, follow-up bias, and other potential sources of bias. In greater detail, the primary criteria evaluated whether a random sequence was employed, whether allocation concealment was implemented, if participant blinding was in place, whether assessors were blinded, the completeness of data, the existence of selective reporting, and the presence of any additional biases. All uncertainties and concerns were thoroughly discussed and successfully resolved during the assessment process.

2.5. Statistical methods

The bias analysis was done by using the bias tool in the Cochrane Handbook for Systemic Interventions 6.4.[10] The meta-analyses were done by using a random effect model with the help of RevMan 5.4 (RevMan 5.4, The Nordic Cochrane Centre, Copenhagen.). Data related to event number and sample size were obtained from the selected studies. The heterogeneity was assessed by the Q test and quantified with I^2test statistics. The combined effect size test adopted u test and 95% Confidential Interval (CI). The p-value with $p<0.05$ is the threshold used for significance. Two separate comparisons for cardiovascular mortality/morbidity were performed: a comparison between Metoprolol and placebo and a comparison between Apixaban and placebo using several events and total sample size. For analyses, if the test showed heterogeneity ($I^2>50\%$) a random effect model was used, or if $I^2\leq50\%$, a fixed effect model was applied. In this study, the M-H method is used to estimate the between-study variation by comparing each study's result due to small sample sizes.

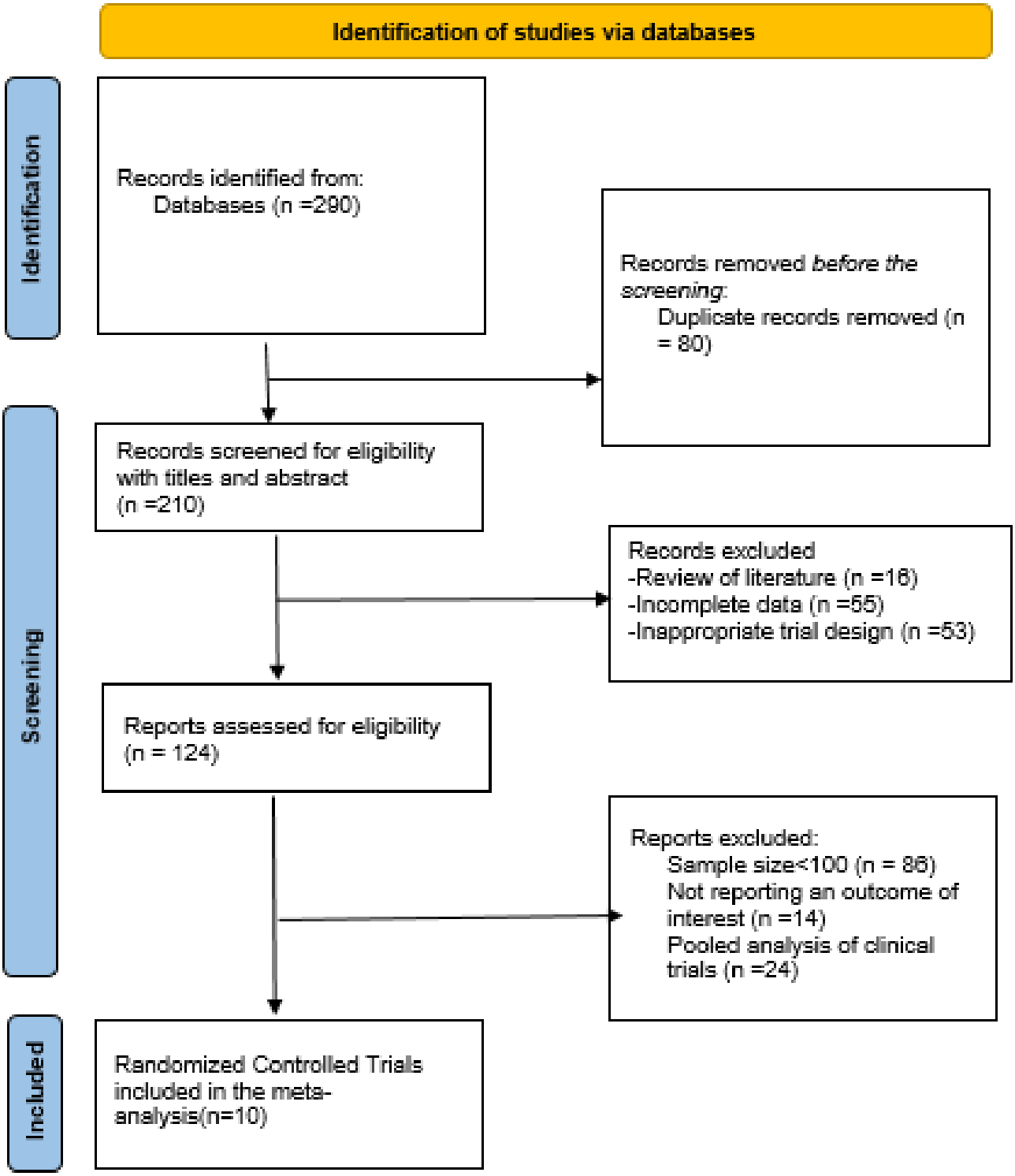

Figure 1: Preferred reporting items for systematic reviews and meta-analysis (PRISMA) flow diagram for study selection.

3. Results

3.1. Article collection and data extraction

A total number of 290 articles were retrieved and 75 remained after the careful read of an abstract session. Last according to the inclusion and exclusion criteria 10 studies (one study with 2 different concentrations of the same drug) with RCTs were finalized for the analysis. (Figure 1) below shows the retrieval process of articles based on inclusion and exclusion criteria, while (Table 1) shows the basic details of the selected articles.

3.2. Bias risk assessment

According to the Cochrane Handbook for Systematic Reviews and Interventions 6.4 (Figure 2) : (a) Random sequence generation- All the 10 articles included used a random method of grouping suggesting a lower risk (b) Allocation concealment – All the 10 articles did not mention whether the blind method was used suggesting unclear risk (c) Blindness of participants- None of the selected studies mentioned whether the participants signed an informed consent form suggesting unclear risk (d) Blindness of the outcome assessors -None of the studies reported whether the outcome assessors blinded suggesting unclear risk (e) Data completeness -All the data were completed one suggesting low risk (f) Selective reporting- None of the selected studies were selective groups suggesting unclear risk (g) Other biases- All references suggesting unclear risk.

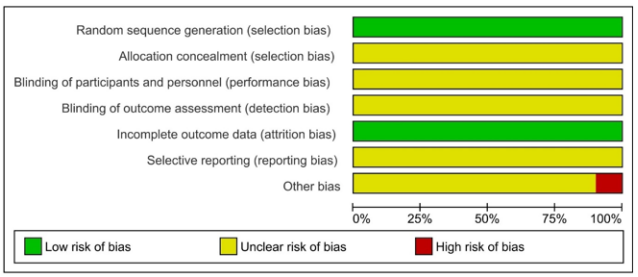

Figure 2: The bias analysis bar chart for selected studies. This bar chart shows that all the selected articles are complete in data, and all are randomly controlled samples, and these are shown in green color. All the selected articles shows an unclear risk of bias in Allocation concealment, the blindness of participants, the blindness of the outcome assessors, selective reporting, and other biases are shown in yellow color. Also, there are some risks in other biases which are shown in red color.

3.3. Cardiovascular mortality/morbidity between Metoprolol and Placebo

The meta-analysis was performed on seven studies that qualified with the required data outcome that could be analyzed quantitatively. The results of the overall

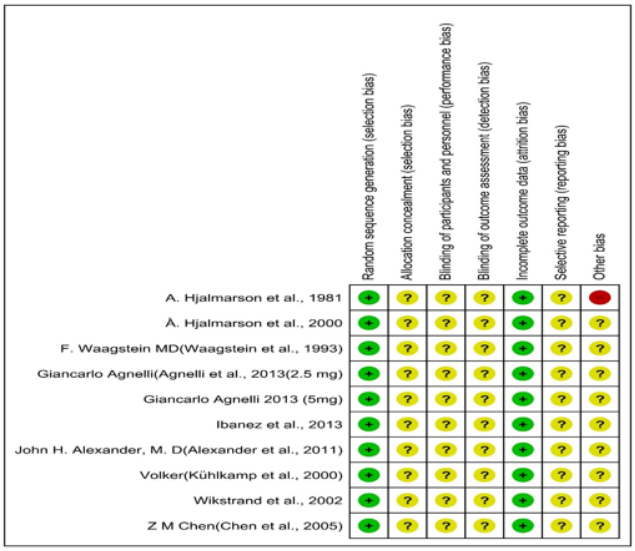

Figure 3: The bias risk assessment results. The figure shows that all the selected articles show some kind of biases (showing in yellow color) except in random selection and completeness of data (showing in green color). Also, there are some bias in one article which is shown in red color.

comparisons have been depicted as a forest plot. Seven studies were included in the meta-analyses comparing Cardiovascular mortality/morbidity between Metoprolol and placebo. With the meta-analysis conducted for selected studies, heterogeneity was more than 50% (I^2= 76%); hence, a random effect model was applied. Cardiovascular mortality/morbidity was significantly less in the Metoprolol group as compared to the placebo group, with an odds ratio of 0.80 (95% CI = 0.67 to 0.95; Z value = 2.50). This difference in Cardiovascular mortality/morbidity among the two groups was statistically significant (p=0.01).

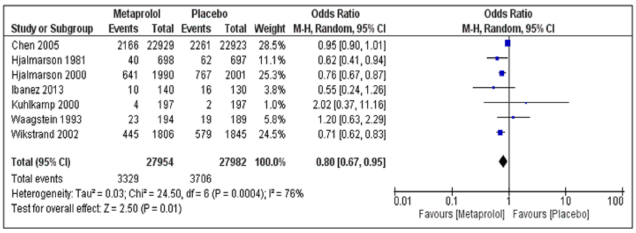

Figure 4: Forest plot displaying all pairwise comparisons for Metoprolol and placebo. (M-H-Mantel-Haenszel statistics, CI-Confidential Interval).

3.4. Cardiovascular mortality/morbidity between Apixaban and placebo

The meta-analysis was performed on two studies that qualified with the required data outcome that could be analyzed quantitatively. The results of the overall

Table 1: Basic details of the selected articles for this meta-analysis study. Totally 10 articles which were followed the inclusion criteria were selected for meta-analysis of both Metoprolol and Apixaban. All the selected articles were shown the outcome of cardiovascular mortality/morbidity.

First author	Year of publication	Number of samples(C/E)	Control group	Observation group	Outcome
Chen [11]	2005	22969/22923	Placebo	Metoprolol	Cardiovascular mortality/ morbidity
Hjalmarson [12]	1981	698/697	Placebo	Metoprolol	Cardiovascular mortality/ morbidity
Hjalmarson [13]	2000	1990/2001	Placebo	Metoprolol	Cardiovascular mortality/ morbidity
Ibanez [14]	2013	140/130	Placebo	Metoprolol	Cardiovascular mortality/ morbidity
Kuhlkamp [15]	2000	197/197	Placebo	Metoprolol	Cardiovascular mortality/ morbidity
Waagstein [16]	1993	194/189	Placebo	Metoprolol	Cardiovascular mortality/ morbidity
Wikstrand [17]	2002	1806/1845	Placebo	Metoprolol	Cardiovascular mortality/morbidity
Agnelli * [18]	2013	840/829	Placebo	Apixaban	Cardiovascular mortality/morbidity
Agnelli [18]	2013	813/829	Placebo	Apixaban	Cardiovascular mortality/morbidity
Alexander [19]	2011	3705/3687	Placebo	Apixaban	Cardiovascular mortality/morbidity

comparisons have been depicted as a forest plot. Two studies with three comparisons were included in the meta-analyses comparing cardiovascular mortality/morbidity between Apixaban and placebo. With the meta-analysis conducted for selected studies, heterogeneity was more than 50% (I^2= 96%); hence, a random effect model was applied. Cardiovascular mortality/morbidity was significantly less in the Apixaban group as compared to the placebo group, with an odds ratio of 0.32 (95% CI = 0.08 to 1.19; Z value = 1.70). This difference in cardiovascular mortality/morbidity among the two groups was statistically non-significant (p=0.09).

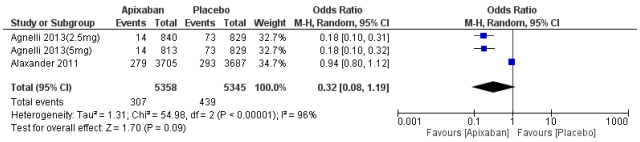

Figure 5: Forest plot displaying all pair-wise comparisons for Apixaban and placebo.(M-H-Mantel-Haenszel statistics, CI-Confidential Interval).

3.5. Publication bias

The RevMan 5.4 software was used to analyze the publication bias in the funnel plot. The funnel plot (Metoprolol vs placebo) shows the effect estimates of the included studies against their measure of precision or size of the studies. The funnel plot shows an asymmetry which indicates heterogeneity and possible publication bias. The funnel plot (Apixaban vs placebo) shows the effect estimates of the included studies against their measure of precision or size of the studies. The funnel plot shows an asymmetry which indicates heterogeneity and possible publication bias.

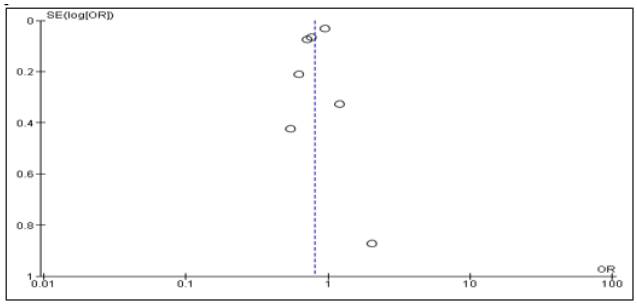

Figure 6: Funnel plot for Metoprolol and placebo which shows the heterogenicity and possible publication bias in the selected articles.

4. Discussion

CVD is a group of diseases that mainly affects the cardiovascular system. [20] According to WHO an estimated 17.9 million people died from CVD in 2019. Patients with CVD or associated situations should have access to appropriate technology and medications including aspirin, beta-blockers, statins, anticoagulants, nitrates, etc., and some surgical operations like heart transplantation, valve

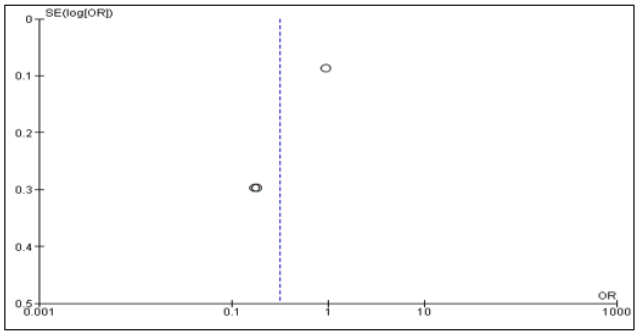

Figure 7: Funnel plot for Apixaban and placebo which shows the heterogenicity and possible publication bias in the selected articles.

repair, coronary bypass, etc. Metoprolol and Apixaban are the two cardiovascular drugs used to treat CVDs. Metoprolol is a beta blocker mainly used to treat angina and hypertension. Metoprolol also blocks the effects of drugs with beta-androgenic agonist activity**.** Apixaban is an anticoagulant which is a direct factor Xa inhibitor that helps to prevent strokes. Metoprolol has a role in reducing heart failure.[21] Thus, these two drugs are widely used to treat CVDs.

This study aimed to systematically evaluate the clinical efficacy of Metoprolol and Apixaban in the treatment of CVD. A total of 10 studies were included and meta-analyses were applied. It was found that cardiovascular mortality/morbidity was significantly less in the Metoprolol group as compared to placebo after treatment. In the case of Apixaban-treated patient's cardiovascular mortality/morbidity was less when compared to placebo. The clinical effectiveness rate was high in drug-treated patients compared to placebo. It is confirmed that Metoprolol and Apixaban help to reduce the intensity of CVD and associated conditions.

5. Conclusions

In conclusion, the use of cardiovascular drugs in the treatment of CVD can effectively reduce the symptoms of patients. This analysis can provide a reference for the treatment of CVD with Metoprolol and Apixaban. The use of both of these drugs is suitable for lowering mortality/morbidity due to CVD. More randomized trials with an effective dose of drugs can be more helpful for the improvement of drug action. There was a large publication bias in some reports and also in some studies the sample size was small, thus the meta-analysis results were not accurate enough. Therefore, it's important to incorporate a large sample size to get a clear report in the future to clarify the efficacy of Metoprolol and Apixaban in the treatment of CVD.

6. List of Abbreviations

1. CI: Confidential Interval
2. CVD: Cardiovascular disease
3. M-H: Mantel-Haenszel statistics
4. RCT: Random Controlled Trials

7. Source of Funding

None.

8. Conflict of Interest

None.

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Author biography

Prajila Mavila, Senior Lecturer https://orcid.org/0009-0002-0279-074X

Mohammad Chand Jamali, Assistant Professor https://orcid.org/0000-0002-1990-0610

Cite this article: Mavila P, Jamali MC. Efficacy of Metoprolol and Apixaban in the treatment of cardiovascular diseases: A meta-analysis. *Indian J Pharm Pharmacol* 2023;10(4):281-287.