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# Management of Multifocal Atrial Tachycardia: Comparison between Beta blockers and Calcium Channel blockers - A Systematic Analysis

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#### Abstract

**Introduction:** Multifocal atrial tachycardia (MAT) is a form of SVT arising from multiple ectopic foci within the atria. The aim is to compare the effectiveness of the two options used in its management.

Methods: This systematic review used a protocol prepared according to the s PRISMA. Google Scholar, MEDLINE (PubMed), and EMBASE, ResearchGate, and Cochrane Library were used

Results: A total of 2,708 patients were included, 955

patients treated with BBs and 1,753 treated with CCBs. 65.65% treated with BBs responded positively to treatment, while 59.50% treated with CCBs responded positively. The effect size of the therapeutic responses was 1.54 [1.29, 1.84] OR at a 95% CI. A test for the overall effect of the two treatment options was Z = 4.84 (P < 0.00001).

Conclusion: Only one certain result was found; both BBs and CCBs can be used in treating MAT with minimal differences in effectiveness or safety.

Keywords: Multifocal Atrial Tachycardia, Beta Blocker, Calcium Channel Blocker, Hypertension

#### Introduction

Multifocal atrial tachycardia (MAT) is a supraventricular tachycardia with a rapid, irregular atrial rhythm arising from multiple ectopic foci within the atria, MAT is characterized by a heart rate of 100 beats per minute.

MAT is an uncommon arrhythmia most often seen in elderly patients with chronic pulmonary disease who are critically ill due to acute respiratory or cardiac decompensation<sup>[1]</sup>.

It has been thought that the long-term force of high blood pressure against the artery wall can lead to other fatal health issues to arise, such as cardiac problems. Multifocal atrial tachycardia (MAT) is a subset of high blood pressure conditions that arises due to irregular atrial rhythm caused by multiple ectopic foci within the atria<sup>[2]</sup>.

MAT is commonly asymptomatic, and its pathogenesis is largely unknown. Therefore, patients will often only be treated for the underlying conditions<sup>[2]</sup>.

The mechanism of the arrhythmia is thought to be triggered activity arising from increased intracellular calcium stores that may be produced by hypokalemia, hypoxia, acidemia, and increased catecholamines, characteristics commonly found in patients with MAT. COPD, coronary artery disease, CHF, and infection (both pulmonary and nonpulmonary) are the most common clinical settings of MAT<sup>[1]</sup>.

Treating MAT requires a correction of the underlying electrolyte abnormalities by repleting magnesium and potassium, thus maintaining them at 2 mEq/L and 4 mEq/L, respectively <sup>[2]</sup>. Magnesium is necessary for suppressing ectopic activity <sup>[3]</sup>. However, once the abnormalities have been corrected, beta-blockers (propranolol and metoprolol) and calcium channel blockers (verapamil and diltiazem) can be used as treatment options<sup>[3]</sup>.

Beta-blockers are necessary for suppressing ectopic foci by decreasing conduction through the atrioventricular node and reducing sympathetic stimulation <sup>[2]</sup>. In other words, beta-blockers reduce the effects of the hormone epinephrine, also referred to as adrenaline. In turn, the rhythm of the heart is corrected into a slower normal heart rate (sinus heart rhythm).

However, despite their usefulness, there are associated risks when beta blockers are used by COPD patients or patients with atrioventricular blocks and without a pacemaker <sup>[2]</sup>. In contrast, using calcium blockers is more recommended to patients with

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underlying pulmonary illnesses like COPD. Despite their reduced success rate compared to beta-blockers (43% versus 79%) as per the findings of Scher and Arsura <sup>[4]</sup>, they tend to harbor less treatment risks. Calcium channel blockers inhibit the entry of calcium into arterial and cardiac cells. This, in turn, decreases conduction through the atrioventricular node, which in turn slows down the ventricular rate <sup>[4]</sup>.

Besides the treatments mentioned above, MAT can also be controlled by improving blood oxygen levels. Medications such as theophylline have been reportedly seen in cases of increased heart rates. Therefore, discontinuing their intake could help treat MAT. Pharmacologic options under calcium channel blocker and beta-blocker categories are numerous. However, their effectiveness and associated risks have not been reviewed extensively. The current literature is not heavily focused on comparing these medications to decide the optimal treatment option. Rather, various standalone studies have investigated the therapeutic effects of individual treatment options.

Verapamil seems to be more focused on by the current literature than any other beta blocker or a calcium channel blocker. Such disjointed evidence regarding effectiveness and safety forms the motivation for of this systematic review.

The investigation team examined various earlier reviews and clinical trials of calcium channel blockers and beta-blockers in treating MAT and, by doing so, compares their effectiveness and safety highlights. The systematic review focuses on two drug alternatives in each category for better comparison. Propranolol and metoprolol represent the betablockers, while verapamil and diltiazem are the calcium channel blockers of concern.

#### Aims of Review

The aim of this systematic review is to investigate the effectiveness of beta-blockers and calcium channel blockers with the aim of making reliable recommendations on which treatment option should be favored in certain situations.

# Methods

#### Protocol

This systematic review used a protocol prepared according to the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA). PRISMA guidelines were adhered to in the inclusion and exclusion of studies, extraction of data, analysis, and discussion of results to ensure the reliability of the findings. This systematic review used the PRISMA extension published in the Cochrane Handbook for systemic reviews and interventions – Chapter 4 by Higgins *et al* <sup>[5]</sup>.

#### Search Strategy

The electronic databases used were the following: Google Scholar, MEDLINE (PubMed), EMBASE, ResearchGate, and Cochrane Library. These five were selected considering the popularity and depth of their library. The search was conducted in January 2022 by one investigator involved in the systematic review. A second party then confirmed their search results before submission for the inclusion and exclusion process.

Initial database searches were conducted electronically using search queries developed using the building blocks technique. Three major keywords, beta-blockers (propranolol and metoprolol), calcium channel blockers (verapamil and diltiazem), and multifocal atria tachycardia (MAT), were used to build the search queries. Additional use of medical subject headings (MeSH), Boolean operators, truncations, and field tags was necessary to increase the database search's precision. Besides an electronic database search, additional studies were located by a hand search through various reference lists.

#### Eligibility Criteria

The inclusion criteria included Randomized control trials (RCTs) despite a scarcity of such RCTs comparing the two therapeutic interventions in treating MAT or any form of cardiac arrhythmia. As a result, studies looking at cardiac resynchronization, atrial fibrillation, and atrial flutter were considered for inclusion. This is because the two conditions, atrial fibrillation and atrial flutter, are subsets of MAT, and they can be treated with beta-blockers or calcium channel blockers. However, RCTs comparing either beta-blockers with a placebo were found.

Any study which fell under this category was included in the systematic review. To build a comparison of performance, included studies had to have reported on the outcome of the cardiac arrhythmia suppression trial. This outcome measure created the basis of our interventional comparison. Time limits were not a limitation for eligibility but allowed the systematic review to include as many useful studies as possible.

The exclusion criteria included the following: letters to the editor, abstracts, non-human or in-vitro studies, and publications that were duplicated, or had data that were poorly extracted or overlapping <sup>[6]</sup>.

# Data Extraction

Three investigators working independently were involved in the extraction of data. Their focus was mainly on the results of the cardiac arrhythmia suppression trial. The investigators encountered reports of the outcome in the included studies either as a return to sinus, heart rate control, or recovery from some form of atrial or cardiac arrhythmia. Data was extracted into a standardized excel sheet prepared before the process. The extraction process focused on study characteristics, patient demographics, methodological approaches, and outcome measures. Results of the extraction were then combined through cordial discussions to modify any incongruities present in the data.

To evaluate the quality of the studies used, a quality assessment was performed using the QUADAS-2<sup>[7]</sup>. Two assessors independently performed quality assessment of said papers. This allowed us to determine bias and applicability, especially because single-arm and non-randomized studies were included in our systematic review and meta-analysis. Studies that fit the inclusion criteria were grouped depending on the similarities they had. Data regarding how the study was designed was also extracted and grouped into three groups: Prospective, retrospective, or unknown. In addition to that, we also looked at the selection of patients, specifically focusing on if it was consecutive or not. Bias verification was a process used and the results were split into three categories: Considerable bias, limited bias, or no bias.

#### Statistical Analysis

Data analysis was performed on Review Manager version

5.4 (RevMan 5.4) software to compare beta-blockers and calcium channel blockers in regard to their ability to suppress cardiac arrhythmia (the definitive trait of MAT). RCTs comparing the two treatment interventions against cardiac arrhythmia were analyzed for standalone results. However, with little to no RCT data making a direct comparison of the two treatment options, the investigation relied, in part, on indirect comparisons from studies testing each against a placebo or control. Pooling findings made indirect comparisons from the active treatment arms of the initial controlled trials. The underside of this approach was, as expected, its disposition to bias.

To counteract this, we used the model proposed by Bucher *et al.* <sup>[8]</sup>; the indirect comparison of the proportional data model was used to preserve the randomization of the originally assigned patient groups in each of the included studies. The increased benefits realized by the comparison were quantified as effect size in an odds ratio at a 95% confidence interval. The systematic review acknowledged the existence of limitations of the strength of interference. However, the statistical analysis did evaluate the magnitude of treatment effect to precision.

A difference in analytical results was calculated by checking the difference in estimated effect size between direct and indirect comparisons. Using the *I*2 statistic, the review measured the level of heterogeneity. A level of heterogeneity  $\leq 50\%$  was considered acceptable to ensure that the included studies were highly homogenous. A funnel plot helped to assess the symmetry of the studies' distribution.

#### Results

#### **Study Selection**

A complete search found 17,944, but after automated filtering, only 1,985 free RCTs comparing beta-blockers to a certain form of calcium channel blocker, which were submitted for the next step. A title and abstract screening were then conducted, eliminating 1,207 studies (778 studies left). However, out of all these, only one study explicitly looked at the treatment of MAT. As a result, studies looking at cardiac resynchronization, atrial fibrillation, and atrial flutter were included. The two conditions, atrial fibrillation and atrial flutter, are subsets of MAT and can be treated with beta-blockers or calcium channel blockers. This consideration eliminated 519 studies and left 259 for further careening.

Exclusion of studies was done according to the following, whether the data reported was incomplete or whether it had not reported our outcome of interest. In most exclusions, studies reported a change in blood pressure. Some studies looked at very long observation periods, which was also grounds for exclusion. This stage eliminated 227 studies meaning that the final stage of the process, which conducted a full-text screening, had 32 studies. Out of these, only 12 studies made it through for inclusion. The PRISMA flow diagram below summarizes the entire process of inclusion. [Figure 1]

#### **Study Characteristics**

The 12 studies assessed a total of 2,708 patients <sup>[9-18]</sup> included in this systematic review. Out of this total, 940 patients were randomized for treatment by beta-blockers, while the remaining 1,741 were randomized for treatment with calcium channel blockers. Two of the included studies

by Haghjoo *et al.* and Hemels *et al.* <sup>[13, 14]</sup> were found to assess the illegible combination of treatment agents. We, therefore, combined them to form an indirect comparison of treatments. Haghjoo *et al.* compared two beta-blockers (carvedilol, metoprolol), while Hemels *et al.* compared a calcium channel blocker to a cardiac glycoside (verapamil, digoxin) <sup>[13, 14]</sup>.

These two studies had similarities on many levels, thus warranting their inclusion as matching studies. The studies were conducted with a difference of one year, with similar population sizes and demographics. In addition to that, both studies had administered similar dosages for the treatment of atrial fibrillation. Moving on, Medeiros *et al.* compared two calcium channel blockers to one beta-blocker <sup>[16]</sup>. The study was pooled into two separate comparisons, thus reviewed as two studies. The table below summarizes these study characteristics <sup>[Table 1]</sup>

# Statistical Results: Therapeutic Response to Treatment Agents

The review results were as follows; 627/955 (65.65%) responded positively to treatment with beta-blockers, while 1043/1753 (59.50%) responded positively to treatment with calcium channel blockers. An effect size of the therapeutic response to the two treatment agents was 1.54 [1.29, 1.84] odds ratio at a 95% confidence interval. A test for the overall effect of the two treatment options was Z = 4.84 (P < 0.00001). However, included studies were very high in heterogeneity with the  $I^2 = 79\%$ . The forest plot shows that 75% of the included studies were symmetrical, having fallen under the inverted funnel. Results of this analysis are represented in the forest and funnel plots in figures 2 and 3 below. <sup>[Figure 2], [Figure 3]</sup>

#### Discussion

Up to this point, it is evident that the two classes of medications have demonstrated an extremely high percentage of treatment success. Beta-blockers and calcium channel blockers lack significant differences in their treatment effectiveness (65.65% versus 59.50%; Difference of 6.15%). All the same, this systematic review shows that beta-blockers had slightly higher treatment effectiveness than calcium channel blockers. There were only four instances; as seen in studies conducted by Demircan *et al*, Hargrove *et al*, McGrath *et al*, and Medeiros *et al*, where calcium channel blockers performed better than beta-blockers  $^{[12, 20, 15, 16]}$ .

In all these studies, metoprolol was compared to diltiazem or verapamil. Among the beta-blockers included in this analytical comparison, esmolol and propranolol seemed to perform best compared to verapamil and diltiazem as reported by Babin-Ebell *et al*, Mooss *et al*, and Platia *et al*, <sup>[9, 15, 16]</sup>. On the other hand, only one isolated case in a study conducted by Arsura *et al*. reported that metoprolol was a better treatment option for MAT than verapamil <sup>[9]</sup>.

After much deliberation, the investigators decided to consider the length of observation to gauge the effect it had on the therapeutic response of the patients. Demircan *et al.* made observations at five intervals (2, 5, 10, 15, and 20 minutes) to determine the difference in therapeutic differences in the comparison of metoprolol with diltiazem <sup>[10]</sup>. Demircan *et al.* observed diltiazem to have more effectiveness against metoprolol at each time interval <sup>[10]</sup>. On the other hand, Mooss *et al.* observed the treatment

response between 6 hours and 24 hours, and both results favoured beta-blocker agents <sup>[17]</sup>. On a different note, Hargrove *et al.* showed that despite the lack of significance in treatment effectiveness between the two agents,metoprolol and diltiazem, their rate to control was different (30 minutes by metoprolol compared to 15 minutes by diltiazem) <sup>[20]</sup>. This outcome was neither analysed by this systematic review nor reported by other included studies. Therefore, it was difficult to make inferences for the review subject.

# Limitations

This systematic review found a lot of results that convincingly pointed to both directions. When these resulted were aligned under one observation, the analytical results did not produce any significant difference to favour either treatment option for MAT or any other cardiac rhythm control condition. On the other hand, the results did demonstrate high effectiveness for treatment by both agents. However, these findings have been limited by various factors along the process. First, the level of heterogeneity in the included studies is extremely high (79%), which is considered to be much higher than the accepted level (50%). Secondly, variability in the treatment agents the various studies included used was seen in many stages of the study. Additionally, the observation periods of these studies lacked uniformity. The indirect comparison did not produce any significant results since the study fell closest to the line of no effect.

Furthermore, scarcity in studies assessing beta-blockers in comparison to calcium channel blockers for the treatment MAT is a limiting factor for the results of this systematic review. More randomized studies are needed to focus on MAT to offer a closer look at this specific rhythm control condition. Also, it would be considered beneficial if future systematic reviews and meta-analyses consider targeting one pair of treatments. Finally, more focus should be given to the safety levels between the two treatment agents following the results of Hargrove *et al.* and Platia *et al.* that showed few safety differences between the two classes of treatments [20, 18].

# Conclusions

This systematic review found that both beta-blockers and calcium channel blockers are effective treatment options for various cardiac rhythm disorders such as MAT. The analytical results pointed slightly in favour of beta-blockers with a 65.65% effectiveness rate of generating positive therapeutic responses. However, with calcium channel blockers showing 59.5% treatment effectiveness, this systematic review cannot offer conclusive inferences as to which treatment agents should be favoured in treating MAT. Only one certain result was found from this investigation; both beta-blockers and calcium channel blockers can be used in treating MAT with minimal differences in effectiveness or safety.

# List of Abbreviations

- MAT: Multifocal Atrial Tachycardia.
- COPD: Chronic Obstructive Pulmonary Disease.
- PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis.
- RCT: Randomized Control Trial.
- QUADAS: Quality Assessment of Diagnostic Accuracy

Studies.

# Conflict of Interest: None.

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