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THE EFFECTIVENESS OF BETA-BLOCKERS VERSUS CALCIUM CHANNEL BLOCKERS IN RATE CONTROL OF ATRIAL FIBRILLATION IN AN EMERGENCY DEPARTMENT: A SYSTEMATIC REVIEW

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Atrial fibrillation, Arrhythmia, Calcium channel blocker, adrenergic antagonist, Beta-blocker, Emergency department

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ABSTRACT: Background: Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. It is related to increased stroke, heart failure, and hospital admission. Therefore, this systematic review was conducted to compare the effectiveness of calcium channel blockers (CCB) with beta-blockers (BB) for acute rate control of AF in the emergency department. **Methods:** We systematically retrieved articles written in English until December 2018 G.C. from the following databases: Embase, PubMed/Medline, Web of Science, and Google Scholar. A preferred reporting item for systematic reviews and meta-analysis (PRISMA) protocol was used. **Result:** Out of eight hundred two studies, three studies met our inclusion criteria with sufficient data. These studies were randomized double-blinded (n=152), comparing CCB with BB. The systemic review revealed that diltiazem was highly effective in reducing ventricular rate compared to metoprolol at each time interval (SMD=-0.78; 95%CI: -1.21 to -0.35). Adverse events were rare and similar, but calcium channel blockers reduced arrhythmia-related symptoms. **Conclusion:** There were insufficient data and a paucity of controlled clinical trial data. A well-designed and high-quality randomized study is needed.

INTRODUCTION: Atrial fibrillation (AF) is the most frequently encountered cardiac dysrhythmia in emergency departments (EDs) in the USA. It is the reason for greater than 500,000 ED visits each year [1].

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Approximately 3–5 million persons in the USA have AF and it is expected to affect >8 million individuals in the USA by 2050 in the elderly population [2, 3]. The European Union anticipated that AF prevalence may rise 8.8 million [4, 5] up to approximately 18 million in 2060 [4, 6].

In line with AF, the National Institute for Health and Care Excellence and European Society of Cardiology guidelines have required additional research on rate control [7, 8] which is also reflected in the level of recommendations from the American Heart Association [9].

Approximately 60%-70% of patients with AF present to EDs with the rapid ventricular response (RVR) [10]. The main treatment modalities for atrial fibrillation (AF) are controlling rate, subsequent rhythm control, and thromboembolism prevention. Beta-blockers (metoprolol, propranolol and esmolol), calcium channel blockers (verapamil, diltiazem), digoxin, or amiodarone may be given a control rates in the emergency department [11].

The study indicates that several patient factors like heart failure, ejection fraction, lung disease, and other comorbidities must be considered when managing atrial fibrillation [12, 13]. The choice of a drug for rate control should be done according to the results of randomized control trials, patient choice, and the presence of other diseases or comorbidities [11]. Data on the comparative efficacy of CCB and BB or between drugs within each class are rare. Therefore, this systemic review presents current evidence on whether CCB (Diltiazem) or BB (Metoprolol) is highly effective for rate control in atrial fibrillation in an emergency department.

METHODS:

Data Sources and Search Strategy: This systematic review was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA 2009) with 27 item checklists [14]. Incorporated studies were done in Norway, USA and Turkey. A flowchart of literature selection was presented in **Fig. 1**.

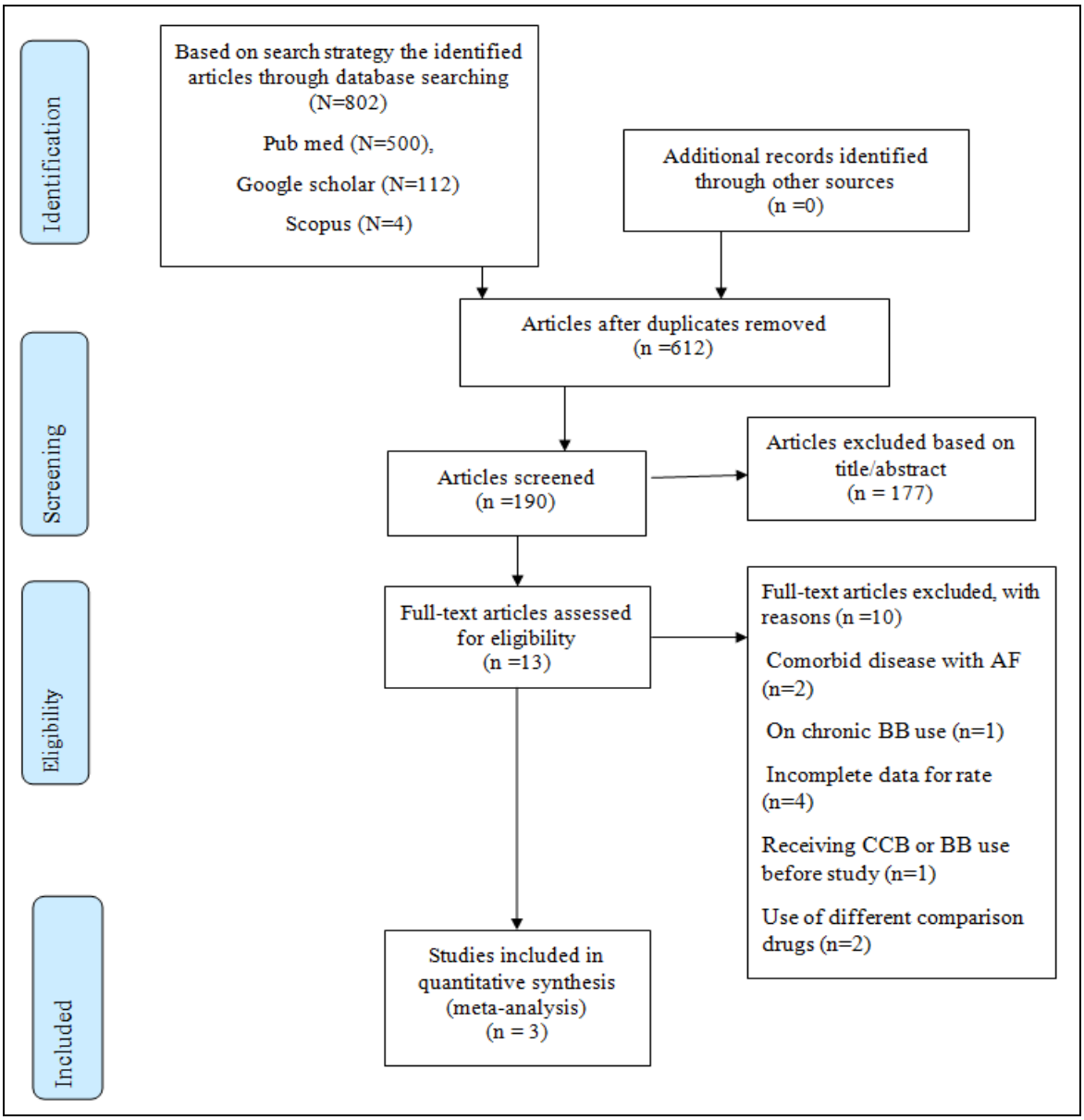

FIG. 1: FLOW CHART OF ELECTRONIC SEARCH FOR STUDY SELECTION. AF, ATRIAL FIBRILLATION; BB, BETA BLOCKER; CCB, CALCIUM CHANNEL BLOCKER

Study Types: Randomized controlled studies.

Inclusion and Exclusion Criteria: Randomized controlled studies, rapid ventricular responses, and studies targeted to reduce ventricular rate and conversion to sinus rhythm are included. Studies addressing AF management as a whole, non-randomized abstracts, studies not published in the English language, patients with postsurgical or post-myocardial infarction, atrial fibrillation, AF with heart failure, and unstable atrial fibrillation are excluded.

Search Strategy:

We Searched Articles Written in English from the following Databases: Embase, Pub Med/ Medline, Web of Science and Google Scholars with a systematic search query.

Study Selection: From a total of 802 articles identified by the literature search, 177 potentially relevant articles were abstracted. After applying the inclusion-exclusion criteria listed above, 3 articles were found to be relevant in **Fig. 1**.

Two investigators independently reviewed each study's abstract with prespecified inclusion and exclusion criteria. In case of disagreement on the article's quality, two authors discussed In front of the table in the third and fourth authors' presence.

Demircan *et al*., 15 Fromm *et al*., 16 and Ulimoen *et al*. 17 provided sufficient information to compare CCB relative to BB in achieving acute rate control in atrial fibrillation.

Among the twelve studies reviewed, six studies Vinson *et al.,* [18] Desai *et al.,*[19] Atzema *et al.,*[20] Feeney *et al.,*[21]Scheuermeyer *et al.,*[22] and Hines *et al.* [23] provided insufficient data and prior use of BB or CCB while one study was done by Scheuermeyer *et al*. [24] was non-randomized.

Vinson *et al.*[18] reported ventricular rate reduction but there is no baseline information for ventricular rate and the result presented is not statistically reported.

Desai *et al.* [19] reported only the percentage of patients achieving rate control at the end of the follow-up period, while Atzema *et al.*[20] reported the predictors for the use of BB or CCB and the choice of medication was dependent on disease comorbidity. Feeney *et al.*[21] reported ventricular rate reduction in patients who used prior BB only, and they also included patients with the comorbid disease.

Scheuermeyer *et al.,* [22] and Hines *et al.*[23] reported ventricular rate reduction in comorbid disease conditions and a predictor for choosing CCB or BB rather than comparing the effectiveness of drugs.

Data Extraction:

Two Investigators Abstracted the Following Parameters About Each Study: Mean age, name of the first author, year of publication, number of patients included in the study, name of the regimen used, doses, route of administration and outcomes reported from all included studies. The available data about adverse events were collected separately; a second investigator checked these data for accuracy. Disagreements among us are managed through discussion in the presence of other authors.

Data Items/Variables: Mean age, name of the first author, year of publication, number of patients included in the study, name of the regimen used, doses, route of administration, and outcomes are used as data items.

Outcomes: The primary endpoint measure was the decrease in ventricular rate (< 100 beats/min) at a specific time defined by the included studies. Both decreases in ventricular rate and conversion to sinus rhythm were considered effective means of achieving rate control. Our secondary endpoint measures were the rate of adverse events and hospitalization associated with the use of medications.

Quality Assessment: Three investigators assessed the reviewed studies for appropriateness in randomization, baseline comparison, blinding, and completeness of outcome data. **Table 1** indicates the risk of bias using the current Cochrane tool for risk of bias in randomized trials using RoB 2.0 tool.

Data Synthesis and Analysis: We qualitatively described and summarized the evidence in the narrative in table and figure forms based on treatment and outcome type.

TABLE 1: RISK OF BIAS JUDGMENTS FOR BIAS ARISING FROM THE RANDOMIZATION PROCESS IN INCLUDED STUDIES USING THE ROB 2.0 TOOL

Bias	Demircan [15]	Fromm [16]	Ulimoen [17]
Random sequence generation	Y	Y	Y
Allocation concealment	Y	Y	Y
Blinding of participants and personnel	Y	Y	Y
Blinding of outcome assessment	Y	Y	Y
Incomplete outcome data	NI	NI	NI
Selective reporting	Y	Y	Y
Were there baseline imbalances that suggest a problem with the randomization process	PN	PN	N
Authors judgment	low	low	low

Y/PY = "Yes" or "Probably yes"; N/PN = "No" or "Probably no"; NI = "No information."

TABLE 2: CHARACTERISTICS OF INCLUDED STUDIES REGARDING THE EFFECTIVENESS OF CCB VS. BB IN ATRIAL FIBRILLATION

	Demircan[15]	Fromm[16]	Ulimoen17
Yr. of publication	**2005**	**2015**	**2013**
Mean age (yr.)	62±12.9	66±13.4	71±9
Total participants	40	52	60
Study Name	Comparing the effectiveness of IV diltiazem and metoprolol	Diltiazem vs. Metoprolol in the Management of AF with RVR in the ED	Compare Four single-drug regimens on VR and arrhythmia-related symptoms in patients with AF
Aim of the study	Compare the effectiveness of IV diltiazem and metoprolol	Compare the effectiveness of diltiazem with metoprolol for rate control of AF in the ED	Compare the effect of 4 rate drug regimens on the VR and arrhythmia-related symptoms in patients with AF
Study design	Prospective, double-blind, randomized study	Prospective, randomized, double-blind trial	Prospective, randomized, investigator-blind, crossover study
Primary outcome	VR of less than 100 beats/min or a 20% decrease in VR	HR < 100 bpm within 30 min of drug administration	lenient rate control,HR <110 beats/min
Results	The rate control effect began earlier, and the percentage decrease in VR was higher with diltiazem than with metoprolol	Diltiazem was more effective in achieving rate control in ED patients with AFF and did so with no increased incidence of adverse effects	CCB performed better than BB on heart rate and arrhythmia-related symptoms

AF; Atrial fibrillation, BB; Beta-blocker, CCB; Calcium channel blocker, ED; Emergency department, HR; Heart rate, IV; Intravenous, RVR; Rapid ventricular rate, VR; Ventricular rate.

Evidence on Comparison of CCB Relative to BB in the Emergency Department: Evidence comparing the effectiveness of beta-blockers (BB) and calcium channel blockers (CCB) as a drug of choice for rate control of atrial fibrillation is limited, but we reviewed different literatures and trials done on rate controlling drugs in atrial fibrillation.

RESULTS:

Study Characteristics: Atrial fibrillation patients attending an emergency department with VR of at least 120 beats /min were included in two articles [15, 16]. Data for comparison of baseline variables like coronary artery disease, AF history, or left ventricular fraction were not addressed in two articles [15, 16]. Baseline heart rates of 150 and 154 beats/min were measured as the median in the metoprolol and diltiazem arms, respectively [15]. Patients with CHF (NYA class 4), CHF (NYA Class IV), 2nd or 3rd AV block, VR>220 beats/min, QRS duration>0.08s, unstable angina, acute myocardial infraction (AMI), hyperthyroidism, fever, anemia, asthma, COPD, DM, pregnancy, history of taking diltiazem, verapamil, digoxin, BB, theophylline and those who took beta-agonists within 5 days were excluded by Demircan *et al.* study [15].

Baseline HR of 142.2 beats/min and 136.8 beats/min was measured as mean in the metoprolol and diltiazem arms, respectively. The mean age and

blood pressure reports were similar in both treatment arms [16]. Patients with congestive heart failure (NYA class IV), asthma history or COPD, early administration of diltiazem, SBP < 90 mm Hg, VR >220 bpm, QRS >0.100s, 2nd or 3rd degree AV block, hyperthermia, acute ST-elevated myocardial infraction, cocaine or methamphetamine use in the 24 hours before arrival, allergic history for diltiazem or metoprolol, pregnancy and breastfeeding, anemia were excluded by Fromm *et al.*[16]. Patients with permanent AF for a duration of longer than 3 months, resting HR >80 beats/min and an average heart rate of >100 beats/min during the day were included. In contrast, patients with CHF or IHD who needed BB as concomitant therapy, hypotension, treatment with class I or III antiarrhythmic drugs, severe renal or hepatic failure, and pregnancy were excluded from Ulimoen study [17]. This study recruited participants with outpatient clinic at Baerum Hospital, Norway. Data for comparison of baseline variables like coronary artery disease, AF history, or left ventricular fraction were not addressed. The 24-hour mean heart rates were 96 ± 12 bpm at baseline (no treatment), 75 ±10 bpm (diltiazem), 81±11bpm (verapamil), 82±11bpm (metoprolol) and 84 ±11 bpm (carvedilol). The doses used for studies were presented in **Fig. 2.**

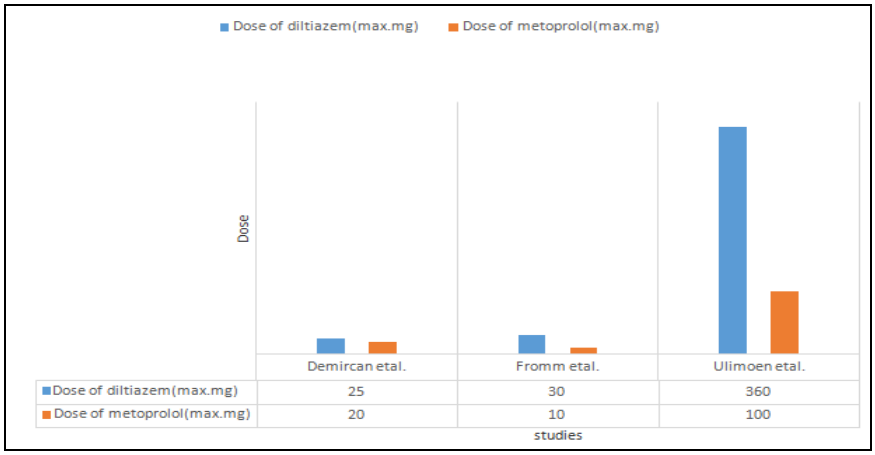

FIG. 2: DOSE OF DILTIAZEM *VS.* METOPROLOL USED BY DIFFERENT STUDIES IN RATE CONTROL OF AF IN THE EMERGENCY DEPARTMENT

Trial Quality: Two conducted studies were registered in clinicaltrials. gov. with ID numbers NCT01914926 [16] and NCT0031357 [17] respectively, but the remaining studies were not registered in clinical trials [15]. A study conducted by Demircan [15] was a prospective, double-blind, randomized study in the emergency department of Uludag University, Turkey. Methods of allocation concealment and blinding were defined. A sample size estimate and baseline comparisons were not reported in this study, but follow-up was complete. There was no report regarding whether or not an intention to treat analysis was used to estimate treatment effect.

A study conducted by Fromm [16] was prospective, randomized, double-blind trial study in adult ED patients with rapid AFF which was undertaken in New York and sequence allocation, allocation concealment and follow-up completion were described but ITT analysis was not used to estimate the treatment effect. A study done by Ulimoen *et al.*[17] was a prospective, randomized, investigator-blind, crossover study designed to compare four drug regimens undertaken in Norway and described methods of allocation concealment and blinding. A predetermined sample size estimate and baseline comparisons were reported in this study, and follow-up was complete. Unlike the above studies, ITT analysis was not used to estimate the treatment effect.

Analysis of Primary Endpoints: The primary endpoint described by Demircan *et al.*[15] was VR<100 beats/min or 20% decrease in VR, which was achieved in 18/20 (90%) patients who received diltiazem and 16/20 (80%) patients who received metoprolol at the end of 20 minute study period. None of them achieved sinus rhythm. The heart rate was greater in the diltiazem group at two minutes (50% *vs.* 15%, $p < 0.05$) and the

proportional decrease in VR at each time was greater in the diltiazem group. In the study by Fromm *et al.*[16] the primary endpoint was HR < 100. The Diltiazem arm (95.8%) and metoprolol arm (46.4%) achieved target HR <100 bpm at the end of 30 min. Neither of them in either treatment arm achieved sinus rhythm during the study period. In the study by Ulimoen *et al.* [17] the successful treatment was defined as a reduction in heart rate (lenient rate control, heart rate <110 beats/min) within 24 hr. Sixty patients (100%) with diltiazem, fifty-six patients (93%) with verapamil, fifty-eight patients (97%) with metoprolol and sixty patients (100%) with carvedilol attained HR at rest (lenient rate control, HR<110 beats/min) within 24 hr. (P<0.001 for all). Thirty-four patients (57%) with diltiazem, twenty-nine patients (48%) with verapamil, thirty-four patients (57%) with metoprolol, and thirty-five patients (58%) with carvedilol satisfied a strict rate control heart rate <80 beats/min. Hence, there was a significant difference in heart rate reduction compared to baseline (p <0.001 for all). There was a significant heart rate reduction in the diltiazem arm compared to other medications tested within 24 hours (p <0.001). Both symptom frequency (p <0.001) and severity (p = 0.005) was reduced significantly with diltiazem use. However, there was a significant association between verapamil treatment and reduction of symptom frequency (p = 0.012). There was no significant difference within metoprolol and carvedilol arm in improving the frequency and severity of symptoms compared to baseline.

Analysis of Secondary Endpoints: Hypotension, as defined by SBP< 90 mmHg, or bradycardia was not experienced among patients in the study conducted by Demircan *et al.* [15]. In the study done by Fromm *et al.* [16] five patients in the metoprolol arm and one patient in the diltiazem arm experienced hypotension (p = 0.199); one patient experienced bradycardia in the diltiazem arm but not in the metoprolol arm (p = 0.462). Hence, there was no significant difference in hypotension and bradycardia.

Findings of the Meta-analysis:

Pooled Estimate Standardized Mean Difference (SMD): This meta-analysis revealed that diltiazem was highly effective in reducing ventricular rate compared to metoprolol (SMD=-0.78; 95%CI: -1.21 to -0.35). This doesn't mean that metoprolol is less effective than diltiazem when used at an emergency department during the trial time.

The negative sign indicates the drug (diltiazem) reduced ventricular rate at the last observation time than the comparison treatment (metoprolol) indicated in **Fig. 3.**

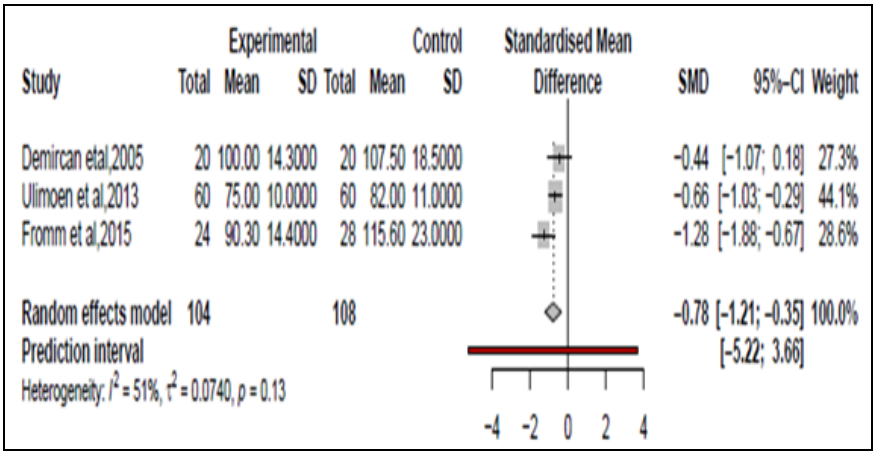

FIG. 3: FOREST PLOT SHOWING HETEROGENEITY AMONG INCLUDED STUDIES

In **Fig. 3**, each squared box indicates the sample size of individual studies. The horizontal line in the middle of each box indicates individual studies' 95% confidence interval. The dot in the middle of the square box and the horizontal line indicate individual studies' effect size (SMD). The long horizontal line inside the squared box, which is wider than the squared box, indicates the sample size is smaller than expected. The diamond shape at the end of the broken vertical line indicates the pooled effect size (pooled PMR). The red color horizontal line shows the prediction interval. The forest plot shows moderate heterogeneity (I^2 = 51%).

However, the p-value (p=0.13) indicates no significant heterogeneity. Therefore, further analysis (subgroup, sensitivity and meta-regression) is not necessary. In addition, the number of studies (3) is not enough to do further analysis, as elaborated in **Fig. 3**.

Publication Bias: The funnel plot (subjective test) seems symmetrical (meaning no publication bias). A more objective test, a linear regression test of funnel plot asymmetry, indicates no evidence of publication bias (p=0.8032) for trim and fill analysis, as illustrated in **Fig. 4**.

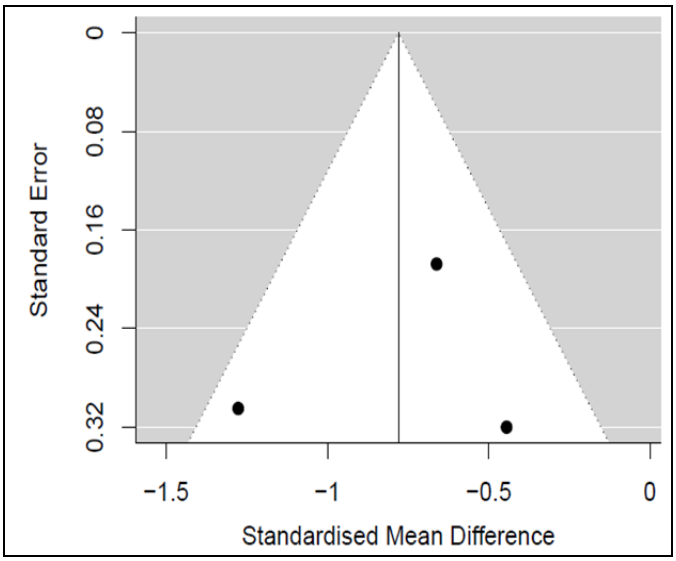

FIG. 4: A FUNNEL PLOT SHOWING SMALL STUDY EFFECT (PUBLICATION BIAS)

DISCUSSION AND CONCLUSION: In the outpatient setting, where rate control may be more important for avoiding tachycardia-related cardiomyopathy, β-blockers are more effective than calcium channel blockers in achieving rate control in atrial fibrillation [25]. In the postoperative setting, diltiazem is more effective than metoprolol in achieving rate control after non-thoracic surgery [26].

Our meta-analysis suggests that in the ED, diltiazem is more effective than metoprolol in rapidly controlling ventricular rates. Diltiazem both slows conduction through the AV node and prolongs the refractory period of AV nodal tissue by blocking L-type calcium channels; metoprolol works more indirectly by blocking sympathetic input to the AV node. Our meta-analysis indicates diltiazem's superior efficacy in emergency departments; however, it is restricted to three articles.

A study by Fromm C *et al.*[16] and colleagues showed that there was a significant difference between diltiazem (95.8%) and metoprolol group (46.4%) groups in attaining the target HR< 100 bpm within 30 minutes (p < 0.0001). Moreover, patients in the diltiazem group (50%) achieved heart rate control compared to the metoprolol group (10.7%) in the first 5 minutes (p <0.005). This is the highest quality study compared to the two drugs. Diltiazem decreased HR more effectively than metoprolol at all times, including 30 minutes. Similarly, the RATAF II study and the study by Martindale *et al.* concluded diltiazem was the most effective drug for reducing the heart rate [17, 27].

In a retrospective cohort study done on 259 patients at Canadian teaching hospitals, a successful reduction in heart rate was observed with diltiazem [24]. The external validity of the study done by Demircan *et al.*[15] was undermined by its exclusion of patients who have taken oral AV nodal blocking agents within 5 days before randomization. Whereas these patients were presumptively excluded to eliminate the attainable contradictory effects of residual oral agents, atrial fibrillation is not a new diagnosis for most patients in the emergency department. Still, a vital proportion of those patients take BB or CCB at home. As well as such, larger study patients would yield conclusions that have a lot of relevance to an emergency physician. Moreover, the exclusion of diabetes mellitus patients, who are not contraindicated to AV nodal blockers, makes this study less generalizable to acute setting populations.

While several adverse events were not found in this meta-analysis, hypotension was the prominent problem the patients faced while using these drugs. The dose utilized by Demircan *et al.*[15] studies (up to a maximum of 25 mg) is similar to the dose suggested by current guidelines [0.25 mg/kg (actual body weight) IV bolus over 2 min] [28]. The diltiazem dose used on patients was different within the clinical setup. Hypotension was observed in 1/61patients who received 0.2 mg/kg or less, 6/83 patients who received more than 0.2 mg/kg and 0.3 mg/kg or less and 1/36 patients who received more than 0.3 mg/kg [29]. Clinicians typically choose to administer calcium before diltiazem to reduce future hypotension, though this was failing in one prospective study to blunt a

decrease in SBP [30]. In this study, 4/8 patients receiving diltiazem (0.25 mg/kg, maximum 20 mg) became hypotensive, yet three of those patients had borderline initial blood pressure (SBP of < 100 mmHg). These results suggest that hypotension due to CCB might not be dose-dependent and flow from different factors like initial baseline blood pressure. Diltiazem is one of the foremost frequent medications used clinically to slow RVR [30].

Variability in managing rapid ventricular rates related to AF mostly stems from a shortage of proof to guide emergency physicians in selecting the foremost, effective and safest AV nodal blocker. Less clear is, however, that the home use of those agents should issue with the ED physician's selection of AV nodal blockers to attain acute management. Preference for one drug category is variable based on the perceived risk of symptomatic bradycardia and hypotension in patients taking medicine from another drug category. Proof concerning the adverse effects of combining beta-blockers and calcium channel blockers (when one is employed orally at home, the other intravenously within the acute care setting) is missing [31].

In the study done by Demircan *et al.*[15] four patients in the metoprolol group who did not attain rate management by twenty min received intravenous diltiazem; consequent hypotension didn't occur. The safety of administering each kind of AV-nodal blocker serially within the ED (when one agent has been deemed ineffective in achieving rapid rate control) has not been studied.

In Fromm C *et al.* study [16], there have been five metoprolol patients and one calcium channel blocker patient with hypotension (p = 0.199). Bradycardia occurred in one calcium channel blocker patient and failed to occur in the group receiving metoprolol (p = 0.462). There was no difference between the groups regarding hypotension (SBP < 90 mm Hg) and bradycardia (HR < 60 bpm). The available proof comparing beta-blockers and calcium channel blockers for rate management in AF is extraordinarily restricted. A quality assessment of one study enclosed during this review could not be performed as additional detailed methodological information couldn't be obtained. We also recognized that patients involved in the trials were not exclusively representative of real emergency department patients with AF due to selective inclusion criteria. Generally, the number of studies included in this meta-analysis is too small, that is, restricted to three articles that lack prior sample size determination and have restricted generalizability, and used small sample sizes, so the findings were based on the small number of studies available. The result of this meta-analysis demonstrates that there were significant differences in the populations recruited, design issues and methodology employed regarding measurement time for ventricular rate reduction in each study. The included studies compare different types of CCB and BB drugs, so there might be a difference in the mode of action for each drug class, and they were using different drug formulations. Therefore, it leads our conclusion to be general for both the class of drugs respective of each drug class and the dosage formulation. Although we performed a meta-analysis in limited literature, we concluded that diltiazem was highly effective than metoprolol in rate control of AF in the emergency department.

Prospective, randomized, and sound trials with larger preset sample sizes should be conducted in future studies to verify the conclusions of our review and newer drug choices in emergency departments. A study that included patients already taking Av nodal blocking agents would be more generalizable to the ED population.

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Authors' Contributions: BB and BH have framed the format design; BB has conceived the review project, conducted the review and developed the manuscript for publication, BB and AM participated in the literature review and format design, participated in the literature review, and BB; FN polished the language of the manuscript. All authors read and approved the final manuscript.

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Availability of Data and Materials: This is a systematic review, and we have used only published articles. The search strategy is provided.

Declarations:
Ethics Approval and Consent to Participate: Not applicable.

Consent for Publication: Not applicable.

CONFLICTS OF INTEREST: The authors declare that they have no competing interests.

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