Original Article

Comparison of diltiazem and metoprolol for atrial fibrillation with rapid ventricular rate: Systematic review and meta-analysis

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ABSTRACT

Background: Intravenous calcium channel blockers or beta-blockers are the preferred rate control medications for hemodynamically stable patients with atrial fibrillation with rapid ventricular rate (AF-RVR) in the emergency department.
Objectives: To compare the efficacy of intravenous diltiazem and metoprolol for rate control and safety with respect to development of hypotension and bradycardia in patients with AF-RVR.
Methods: For this systematic review and meta-analysis, we searched PubMed, Embase, Cochrane databases, and the clinicaltrials.gov registry between database inception and 30th May 2021. Articles were included if they compared efficacy and safety of diltiazem versus metoprolol in critically ill adult patients hospitalized with AF-RVR. Outcome measures were achievement of rate control, development of new hypotension, and bradycardia after drug administration.
Results: Of 86 records identified, 14 were eligible, all of which had a low to moderate risk of overall bias. The meta-analysis (Mantel-Haenszel, random-effects model) showed that diltiazem use was associated with increased achievement of rate control target compared to metoprolol [14 studies, n = 1732, Odds Ratio (OR): 1.92; 95% Confidence Intervals (CI):1.26 to 2.90; $I^2 = 61\%$]. In the pooled analysis, no differences were seen in hypotension using diltiazem vs metoprolol [12 studies, n = 1477, OR: 0.96; 95% CI:0.61 to 1.52; $I^2 = 35\%$] or bradycardia [9 studies, n = 1203, OR: 2.44; 95% CI: 0.82 to 7.31; $I^2 = 48\%$].
Conclusions: Intravenous diltiazem is associated with increased achievement of rate control target in patients with AF-RVR compared to metoprolol, while both medications are associated with similar incidence of hypotension and bradycardia.

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia leading to emergency department (ED) visits. Consensus guidelines suggest that most patients with AF can be safely managed in the emergency department without the need for hospital admission.[1] For emergency patients with Atrial Fibrillation (AF) with Rapid Ventricular Rate (RVR), a strategy of either rate control or rhythm control could be selected based on multiple factors including the duration of AF and hemodynamic stability. When the duration of AF is > 48 h or uncertain, ventricular rate control with non-dihydropyridine

calcium channel blockers or beta-blockers is the preferred initial strategy for hemodynamically stable patients. Intravenous diltiazem and metoprolol are commonly used to achieve rate control in patients with atrial fibrillation with rapid ventricular rate. No comprehensive review is available of the evidence regarding the impact of the choice of diltiazem compared to metoprolol on the achievement of desired rate control target and hemodynamic adverse events with the use of these medications in the emergency department. The current review was undertaken to inform emergency physicians on the choice of medication for rate control in patients with atrial fibrillation with rapid ventricular rate presenting to the emergency department based on the available evidence. The purpose of this review was to assess whether there was an association between the use of intravenous diltiazem versus metoprolol for rate control in AF with RVR patients, with successful rate control and hemodynamic adverse events, in particular, hypotension and bradycardia.

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2. Objectives

The primary objective of this systematic review and meta-analysis was to compare the efficacy of intravenous diltiazem and metoprolol for rate control in patients with atrial fibrillation with rapid ventricular rate. The secondary objective was to evaluate the safety of intravenous diltiazem and metoprolol in patients with atrial fibrillation with rapid ventricular rate, with respect to the development of new hypotension and bradycardia after administration of these medications.

3. Methods

ELIGIBILITY CRITERIA- Articles were included if they compared efficacy and safety of intravenous diltiazem versus metoprolol in adult (age ≥18 years) patients with atrial fibrillation with rapid ventricular rate in the emergency department or intensive care unit. To be included, the study had to use a defined clinical outcome relating to efficacy (achievement of rate control target) and safety (hypotension or bradycardia occurring as an adverse event) of the two medications. Our primary outcome measure was the achievement of ventricular rate control <110/min in patients hospitalized with atrial fibrillation with rapid ventricular rate, and secondary outcomes were development of new hypotension (systolic blood pressure <90 mm Hg) and bradycardia (heart rate <60/min) after administration of intravenous diltiazem or metoprolol. There were no restrictions on study design. Articles were excluded if they studied oral medications for chronic rate control in outpatients with atrial fibrillation. We also excluded articles, if they studied management of atrial fibrillation in patients with pre-excitation syndromes.

4. Information sources

One investigator (SCS) designed and conducted a comprehensive search of the following electronic databases and trial registers- PubMed, Embase, Cochrane, and clincaltrials.gov up to and including 30th May 2021. The strategies used a combination of controlled vocabulary as follows: (a) Medical Subject Headings in PubMed-((atrial fibrillation[MeSH Terms]) AND (diltiazem[MeSH Terms])) AND (metoprolol[MeSH Terms]); (b) Embase- 'atrial fibrillation'/exp/mj AND 'diltiazem'/exp/mj AND 'metoprolol'/exp/mj; (c) Cochrane-atrial fibrillation in Title Abstract Keyword AND diltiazem in Title Abstract Keyword AND metoprolol in Title Abstract Keyword; (d) clinicaltrials.gov-diltiazem metoprolol | Completed Studies | Atrial Fibrillation. No language restrictions were applied and all studies indexed in the databases since their inception were included. We also identified additional studies by searching the reference lists of publications eligible for full-text review. In phase 1, the investigators (SCS and MSB), screened all titles and abstracts for eligibility. Records considered potentially relevant were assessed in full text for eligibility in phase 2 (SCS and MSB).

5. Data analysis

Pertinent data were extracted-citation details; the study site (Emergency Department or Intensive Care Unit); retrospective or prospective study; observational or interventional study; treatment assignment mechanism; details of the intervention; and outcomes of interest. One investigator (SCS) entered the data into Review Manager program. Another investigator (MSB) checked this for accuracy. We assessed the risk of bias in the following specific domains: (a) bias arising from the randomization process; (b) bias due to blinding of participants and personnel; (c) bias due to

blinding of outcome assessment; (d) bias due to missing outcome data; and (e) bias due to selective reporting of the results.[2] The quality of evidence was evaluated with the Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence document and graded from Level 1 (High Quality) to Level 5 (Low Quality).[3]

Eligible outcomes were achievement of rate control target and development of new hypotension and bradycardia after administration of intravenous diltiazem or metoprolol. The primary efficacy endpoint of achievement of rate control target was defined as ventricular rate <110/min within 6 h of intravenous administration of diltiazem or metoprolol. Where multiple outcomes were reported, we selected one outcome for inclusion in the analysis, choosing the result that provided the most relevant information (e.g., sustained rate control at 2 h was prioritized over rate control at 5min). With respect to safety endpoints, hypotension was defined as SBP <90 mm Hg, and bradycardia as heart rate <60/min within 6 h after the administration of rate control drugs.

We considered it reasonable to pool the data from Emergency Department and Intensive Care Unit studies to have a better understanding of the comparative outcomes with the use of diltiazem and metoprolol in patients with atrial fibrillation with rapid ventricular rate in emergency settings. We used Review Manager (RevMan- Computer program, Version 5.4, The Cochrane Collaboration, 2020) for meta-analyses. Dichotomous outcomes were
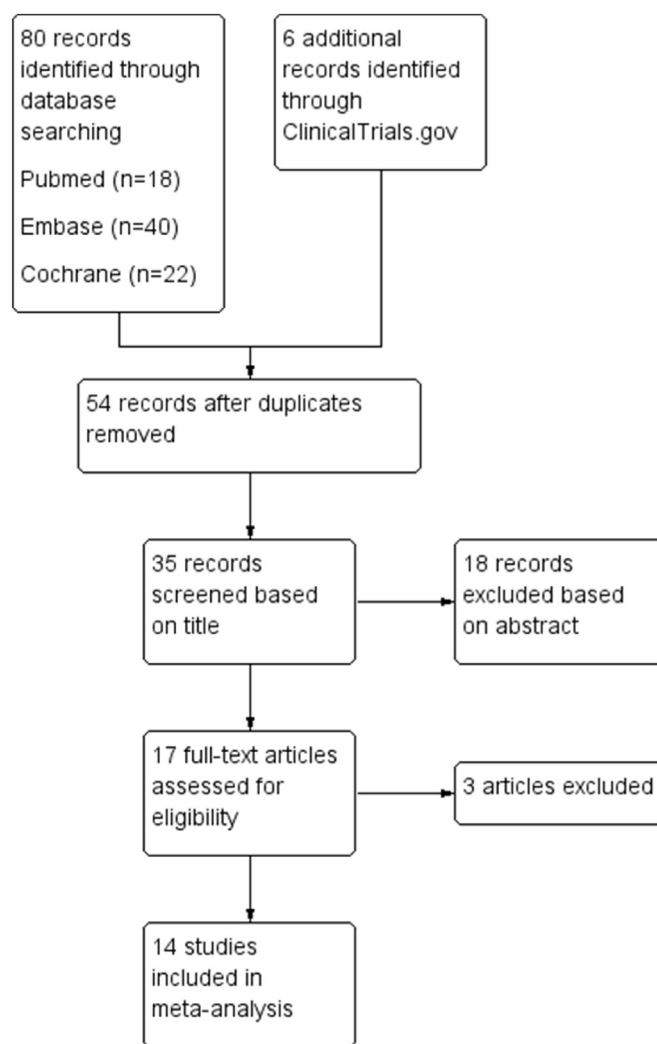

Fig. 1. Systematic database search flow diagram.

assessed for odds ratio (OR) with 95% confidence intervals (CI) using Mantel-Haenszel (M–H) random-effects model to account for the clinical and statistical heterogeneity between studies. P-value < 0.05 indicated statistical significance. The heterogeneity was assessed by visual inspection of Forest Plots, and statistical tests for heterogeneity variance ($\tau2$) and inconsistency (I^2). Heterogeneity was deemed significant if $I^2 > 50\%$.

6. Results

We found 86 records in database and trial registry search (Fig. 1). After duplicate removal and screening titles, we screened abstracts of 35 records, from which we selected 17 studies for full-text review, and finally included 14 studies (Table 1). Details of inclusion criteria, exclusion criteria, doses of diltiazem and metoprolol, and outcome definitions for rate control, hypotension and bradycardia in the included studies are provided in Supplement 1 (Table 2). We collected the outcome data from eleven retrospective studies and three randomized controlled trials. All fourteen studies contained outcome data for achievement of rate control target with diltiazem compared to metoprolol in patients with atrial fibrillation with rapid ventricular rate, twelve studies contained data for the development of new hypotension as an adverse event with diltiazem versus metoprolol, and nine studies contained data for bradycardia as an adverse event. With respect to our primary efficacy endpoint of achievement of rate control target, three of the fourteen included studies- Demircan 2005, Katchi 2014, and Nicholson 2020 defined the efficacy outcome as either ventricular rate control or conversion to sinus rhythm after administration of intravenous diltiazem or metoprolol. We excluded three studies from our review- Lopez 2020[4], Chen 2016[5], and Moskowitz 2017.[6] For Lopez 2020, only the research abstract could be accessed, and complete outcome data were unavailable. We excluded Chen 2016

(Conference Poster Contribution) and Moskowitz 2017, because, in these studies, outcome measures of rate control, hypotension and bradycardia were not assessed and reported.

Fourteen studies, including eleven retrospective studies and three randomized controlled trials (RCTs), directly compared the achievement of rate control target between diltiazem and metoprolol groups (Fig. 2).[7–20] These studies enrolled 1732 patients in emergency departments (thirteen studies) and intensive care unit settings (one study). These fourteen studies were pooled, as they each reported achievement of rate control target with diltiazem (n = 773) compared to metoprolol (n = 959) in patients with atrial fibrillation with rapid ventricular rate. Patients treated with intravenous diltiazem had significantly greater achievement of rate control target compared to patients treated with intravenous metoprolol (odds ratio: 1.92; 95% CI: 1.26 to 2.90; p = 0.002); with significant heterogeneity (I^2 = 61%). Twelve studies, including 1477 patients, reported the rate of hypotension as an adverse event with diltiazem versus metoprolol (Fig. 3).[7–16,18,20] Meta-analysis of outcomes of these twelve studies showed no significant difference in the occurrence of hypotension as an adverse event with diltiazem (n = 647) vs. metoprolol (n = 830) in patients with atrial fibrillation with rapid ventricular rate (odds ratio: 0.96; 95% CI: 0.61 to 1.52; p = 0.87); without significant heterogeneity (I^2 = 35%). Nine studies, including 1203 patients, reported the rate of bradycardia as an adverse event with diltiazem versus metoprolol (Fig. 4).[7,9–16] Meta-analysis of outcomes of these nine studies did not show a significant difference in the occurrence of bradycardia as an adverse event with intravenous diltiazem (n = 505) vs. metoprolol (n = 698) in patients with atrial fibrillation with rapid ventricular rate (odds ratio: 2.44; 95% CI: 0.82 to 7.31; p = 0.11); without significant heterogeneity (I^2 = 48%). A summary of the risk of bias assessments is provided in Fig. 5. Regarding the overall risk of bias, there were concerns about a low to moderate risk of bias for all the

Table 1
Characteristics of included studies.

Author (year)	Study design	Country	Sample size	Source of participants	Interventions		Outcomes			Level of Evidence[a]
					Diltiazem	Metoprolol	Rate Control	Hypotension	Bradycardia	
Demir 2021(7)	Retrospective Comparative	Turkey	50	Emergency Department	✓	✓	✓	✓	✓	3
Demircan 2005(8)	Randomized Controlled Trial	Turkey	40	Emergency Department	✓	✓	✓	✓	X	2
Feeney 2018(9)	Retrospective Comparative	USA	332	Emergency Department	✓	✓	✓	✓	✓	3
Fromm 2015(10)	Randomized Controlled Trial	USA	54	Emergency Department	✓	✓	✓	✓	✓	2
Hargrove 2021(11)	Retrospective Comparative	USA	51	Emergency Department	✓	✓	✓	✓	✓	3
Hines 2016(12)	Retrospective Comparative	USA	100	Emergency Department	✓	✓	✓	✓	✓	3
Hirschy 2019(13)	Retrospective Comparative	USA	48	Emergency Department	✓	✓	✓	✓	✓	3
Katchi 2014(14)	Retrospective Comparative	USA	173	Emergency Department	✓	✓	✓	✓	✓	3
McGrath 2020(15)	Retrospective Comparative	USA	349	Emergency Department	✓	✓	✓	✓	✓	3
Medeiros 2021(16)	Retrospective Comparative	USA	78	Emergency Department	✓	✓	✓	✓	✓	3
Memis 2018(17)	Randomized Controlled Trial	Turkey	100	Emergency Department	✓	✓	✓	X	X	2
Nicholson 2020(18)	Retrospective Comparative	USA	108	Emergency Department	✓	✓	✓	✓	X	3
Nunez Cruz 2020(19)	Retrospective Comparative	USA	160	Emergency Department	✓	✓	✓	X	X	3
Personett 2014(20)	Retrospective Comparative	USA	121	Postoperative patients (Intensive Care Unit)	✓	✓	✓	✓	X	3

[a] Evaluated according to Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence Document with levels from 1 (High) to 5(Low).[3]

Study or Subgroup	Diltiazem Events	Diltiazem Total	Metoprolol Events	Metoprolol Total	Weight	Odds Ratio M-H, Random, 95% CI
Demir 2021	17	28	11	22	6.7%	1.55 [0.50, 4.78]
Demircan 2005	18	20	16	20	3.7%	2.25 [0.36, 13.97]
Feeney 2018	11	16	134	316	7.0%	2.99 [1.01, 8.80]
Fromm 2015	23	24	13	28	2.9%	26.54 [3.14, 224.53]
Hargrove 2021	28	32	15	19	4.8%	1.87 [0.41, 8.54]
Hines 2016	33	51	19	36	8.4%	1.64 [0.69, 3.92]
Hirschy 2019	15	30	8	13	5.7%	0.63 [0.17, 2.36]
Katchi 2014	76	90	72	83	8.6%	0.83 [0.35, 1.95]
Mcgrath 2020	78	183	76	166	11.8%	0.88 [0.58, 1.34]
Medeiros 2021	16	51	3	15	5.3%	1.83 [0.45, 7.39]
Memis 2019	46	50	26	50	6.5%	10.62 [3.32, 33.95]
Nicholson 2020	35	63	16	45	9.1%	2.27 [1.03, 4.98]
Nunez Cruz 2020	43	80	34	80	10.3%	1.57 [0.84, 2.94]
Personett 2014	42	55	35	66	9.1%	2.86 [1.30, 6.29]
Total (95% CI)		773		959	100.0%	1.92 [1.26, 2.90]
Total events	481		478			

Heterogeneity: Tau² = 0.33; Chi² = 33.26, df = 13 (P = 0.002); I² = 61%
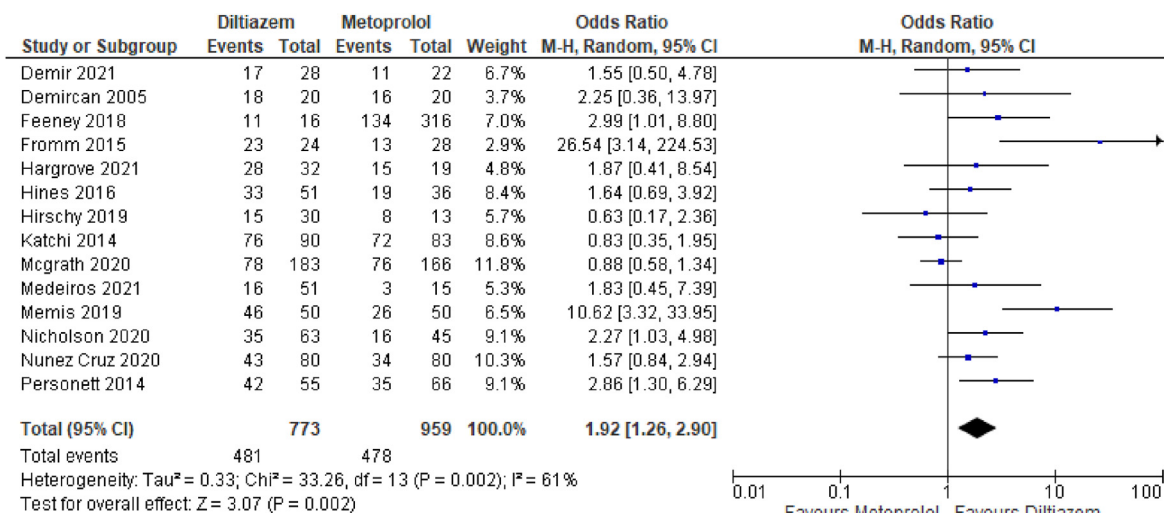Test for overall effect: Z = 3.07 (P = 0.002)

Fig. 2. Forest plot of Rate Control Success with Diltiazem (n = 773) vs. Metoprolol (n = 959) in patients with Atrial Fibrillation with Rapid Ventricular Rate.
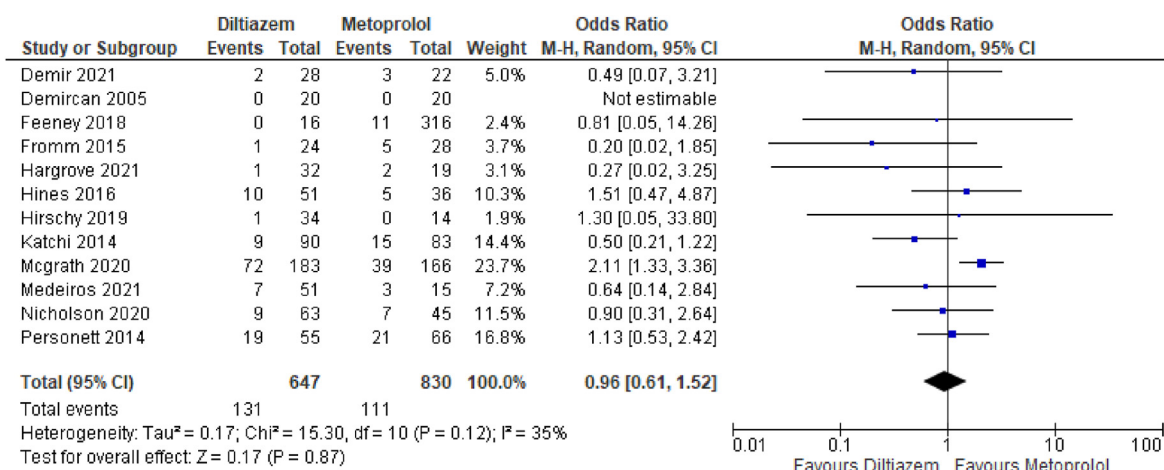
Study or Subgroup	Diltiazem Events	Diltiazem Total	Metoprolol Events	Metoprolol Total	Weight	Odds Ratio M-H, Random, 95% CI
Demir 2021	2	28	3	22	5.0%	0.49 [0.07, 3.21]
Demircan 2005	0	20	0	20		Not estimable
Feeney 2018	0	16	11	316	2.4%	0.81 [0.05, 14.26]
Fromm 2015	1	24	5	28	3.7%	0.20 [0.02, 1.85]
Hargrove 2021	1	32	2	19	3.1%	0.27 [0.02, 3.25]
Hines 2016	10	51	5	36	10.3%	1.51 [0.47, 4.87]
Hirschy 2019	1	34	0	14	1.9%	1.30 [0.05, 33.80]
Katchi 2014	9	90	15	83	14.4%	0.50 [0.21, 1.22]
Mcgrath 2020	72	183	39	166	23.7%	2.11 [1.33, 3.36]
Medeiros 2021	7	51	3	15	7.2%	0.64 [0.14, 2.84]
Nicholson 2020	9	63	7	45	11.5%	0.90 [0.31, 2.64]
Personett 2014	19	55	21	66	16.8%	1.13 [0.53, 2.42]
Total (95% CI)		647		830	100.0%	0.96 [0.61, 1.52]
Total events	131		111			

Heterogeneity: Tau² = 0.17; Chi² = 15.30, df = 10 (P = 0.12); I² = 35%
Test for overall effect: Z = 0.17 (P = 0.87)

Fig. 3. Forest plot of Hypotension as an adverse event with Diltiazem (n = 647) vs. Metoprolol (n = 830) in patients with Atrial Fibrillation with Rapid Ventricular Rate.

included studies, but none of these were assessed as having a high risk of bias.

Subgroup analysis of studies from emergency departments (excluding studies from intensive care unit) included thirteen studies (n = 1611) for the primary outcome of achievement of rate control target with diltiazem compared to metoprolol (Supplement 2). In the subgroup of emergency department patients, diltiazem use was associated with increased achievement of rate control compared to metoprolol (odds ratio: 1.85; 95% CI: 1.19 to 2.87; p = 0.006). Similarly, the single study focused on intensive care unit (ICU) patients showed increased rate control with diltiazem (n = 55) compared to metoprolol (n = 66) (odds ratio: 2.86; 95% CI: 1.30 to 6.29; p = 0.009).

Sensitivity analysis was undertaken for the primary outcome of successful rate control, by including only the three randomized controlled trials comparing diltiazem and metoprolol for atrial fibrillation with rapid ventricular rate (Supplement 3). The results were consistent with the primary meta-analysis, with intravenous diltiazem being associated with increased achievement of rate control target compared to metoprolol (odds ratio: 8.38; 95% CI: 2.46 to 28.52; p = 0.0007).

7. Discussion

The aim of rate control in atrial fibrillation with rapid ventricular response is to reduce symptoms, improve hemodynamics, prevent heart failure and reduce the risk of adverse cardiovascular outcomes.[21] In patients presenting to the emergency department with atrial fibrillation with rapid ventricular response, who are symptomatic but not unstable, initial therapy usually involves rate control with intravenous calcium-channel blockers or beta-blockers. Beta-blockers act by blocking sympathetic activity in the atrioventricular node to slow ventricular rate. Non-dihydropyridine calcium-channel antagonists, such as verapamil and diltiazem, slow atrioventricular node conduction by blocking calcium channels, thereby increasing the refractory period of the atrioventricular node. They are often used as the first-line rate-controlling agents. Intravenous metoprolol is administered as a bolus of 2.5–5.0 mg over 2 min; and may be repeated up to 3 doses.[22] Intravenous diltiazem is given at a dose of 0.25 mg/kg over 2 min. A second bolus may be given after 15 min if the heart rate continues to be more than 100 beats per minute, followed by an infusion at the rate of 5–15 mg/h. This systematic review and meta-analysis compared
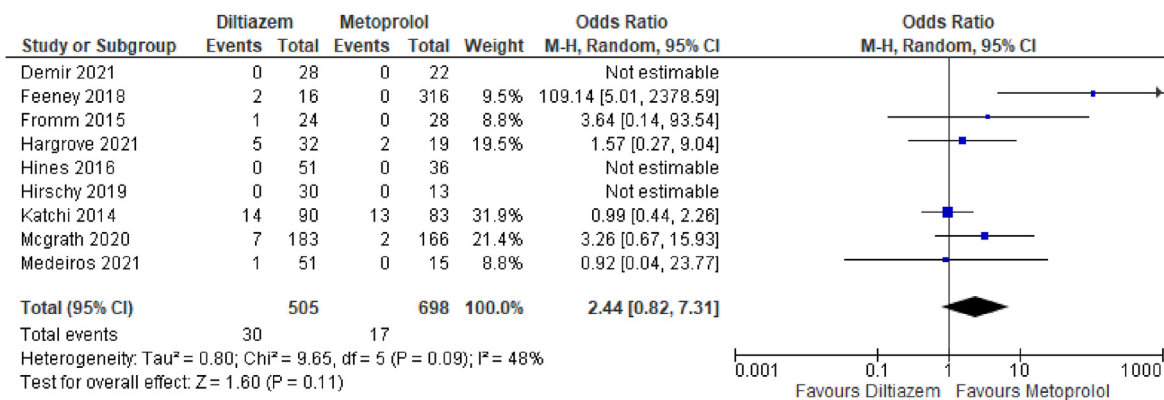
Study or Subgroup	Diltiazem Events	Total	Metoprolol Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Demir 2021	0	28	0	22		Not estimable
Feeney 2018	2	16	0	316	9.5%	109.14 [5.01, 2378.59]
Fromm 2015	1	24	0	28	8.8%	3.64 [0.14, 93.54]
Hargrove 2021	5	32	2	19	19.5%	1.57 [0.27, 9.04]
Hines 2016	0	51	0	36		Not estimable
Hirschy 2019	0	30	0	13		Not estimable
Katchi 2014	14	90	13	83	31.9%	0.99 [0.44, 2.26]
Mcgrath 2020	7	183	2	166	21.4%	3.26 [0.67, 15.93]
Medeiros 2021	1	51	0	15	8.8%	0.92 [0.04, 23.77]
Total (95% CI)		**505**		**698**	**100.0%**	**2.44 [0.82, 7.31]**
Total events	30		17			

Heterogeneity: Tau² = 0.80; Chi² = 9.65, df = 5 (P = 0.09); I² = 48%
Test for overall effect: Z = 1.60 (P = 0.11)

Fig. 4. Forest plot of Bradycardia as an adverse event with the use of Diltiazem (n = 505) vs. Metoprolol (n = 698) in patients with Atrial Fibrillation with Rapid Ventricular Rate.
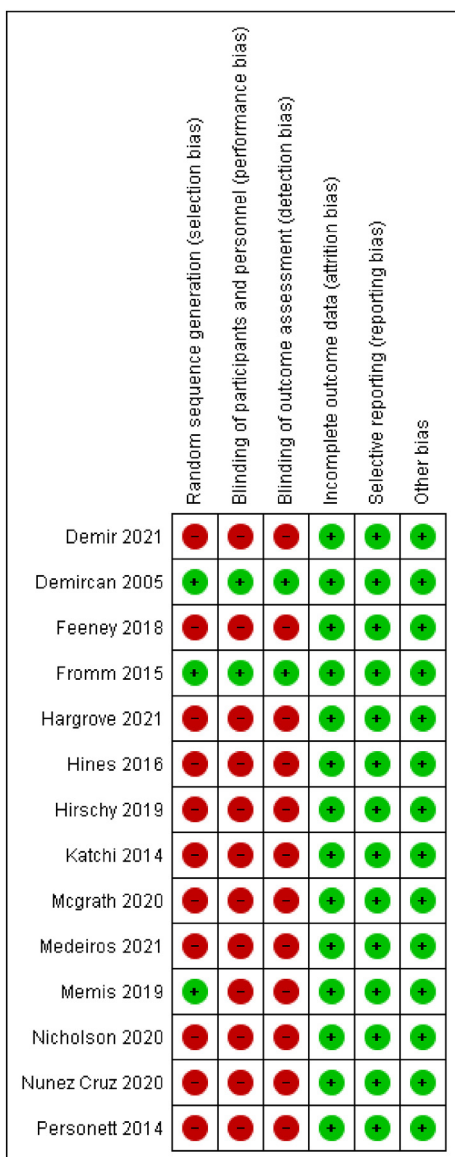

Fig. 5. Risk of bias summary for included studies.

the safety and efficacy of the first-line intravenous rate control medications diltiazem and metoprolol with respect to the achievement of rate control target and adverse events, i.e., hypotension and bradycardia. The certainty of evidence from this meta-analysis is considered moderate, because of concerns for bias due to the largely observational nature of included studies.[23] The results of this meta-analysis favor intravenous diltiazem for significantly better achievement of rate control target compared to intravenous metoprolol in patients with atrial fibrillation with rapid ventricular rate in emergency settings. This is especially important because suboptimal rate control is associated with increased cardiovascular adverse events.[24] However, the result came with significant heterogeneity between the studies. This was primarily due to the results of Hirschy 2019 and Katchi 2014, which showed no significant difference in the achievement of the rate control target between the two groups. Hirschy 2019 studied the effects of diltiazem versus metoprolol in atrial fibrillation with rapid ventricular response in patients with heart failure with reduced ejection fraction (HFrEF), and Katchi 2014 focused on patients with acute decompensated heart failure (ADHF), conditions where the use of non-dihydropyridine calcium channel blockers is not recommended by American College of Cardiology/American Heart Association/Heart Rhythm Society practice guidelines.[22] In patients with a previous history of atrial fibrillation who present to the emergency department with AF-RVR, physicians often favour the intravenous formulation of the patient's oral home rate control medication, which may not be ideal for ventricular rate control in emergency settings.[9,11] Another important consideration is the development of new hypotension and bradycardia after administration of intravenous rate control medications. This meta-analysis showed no significant difference in the incidence of adverse events (hypotension and bradycardia) with the use of intravenous diltiazem and metoprolol for rate control. This result suggests a similar safety profile for both medications for use in patients with atrial fibrillation with rapid ventricular rate. Jafri et al conducted a systematic review and meta-analysis of three studies on paroxysmal atrial fibrillation and found that the mean reduction in heart rate was greater at 5, 10, and 15 min in the group of patients treated with intravenous diltiazem compared to metoprolol, with no significant differences in systolic blood pressures between the two groups.[25] A recent systematic review and meta-analysis by Lan et al also found greater efficacy of intravenous diltiazem compared to metoprolol for rate control at 30 min in atrial fibrillation with rapid ventricular rate, and no significant difference in adverse events.[26] These findings are consistent with the results of the present meta-analysis, and provide important evidence for selecting intravenous diltiazem as the preferred medication for rate control in atrial fibrillation with rapid ventricular rate in the emergency department.

8. Limitations

The studies included predominantly retrospective studies and only three randomized controlled trials. The included studies were often limited by selection bias, small sample sizes, and lack of blinding of personnel and outcome assessment. Functional outcomes, such as 30-day mortality, readmission rates, and worsening heart failure, were not assessed in the present meta-analysis. We did not evaluate the association of comorbidities, such as coronary artery disease, hypertension, diabetes mellitus, obesity, prior stroke or transient ischemic attack, asthma or chronic obstructive pulmonary disease, infections, kidney disease and peripheral vascular disease, with achievement of rate control target and adverse effects with diltiazem and metoprolol use. In addition, the results are not applicable to patients with pre-excitation syndromes as they were excluded from the meta-analysis.

9. Conclusions

Findings from the meta-analysis suggest that the use of intravenous diltiazem is associated with increased achievement of rate control target in patients with atrial fibrillation with rapid ventricular response compared with metoprolol, while both medications are associated with similar incidence of hypotension and bradycardia. These results favour the selection of diltiazem as the preferred agent over metoprolol for rate control in emergency settings. However, our understanding of the impact of choice of rate control medication for atrial fibrillation with rapid ventricular response in the emergency department would further benefit from future high-quality blinded randomized controlled trials that make direct comparisons within subgroups with heart failure with preserved ejection fraction and heart failure with reduced ejection fraction.

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None.

Author contribution

SCS conceived and designed the study. SCS and MSB searched and reviewed the articles for eligibility and extracted the data. SCS performed the statistical analysis and drafted the manuscript, and MSB contributed significantly to its revision. All authors agree to take responsibility for the paper as a whole.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ihj.2022.10.195.

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