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Diltiazem versus metoprolol for the management of atrial fibrillation: A systematic review and meta-analysis

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1. Introduction

Atrial fibrillation (AF) is the most common pathological cardiac arrhythmia, affecting more than 33 million people around the globe [1]. AF is broadly classified based on the duration of cardiac arrhythmia; pAF lasting less than one-week (paroxysmal AF), duration between one-week to one-year (persistenet AF), and duration greater than one-year (long-standing, persistent AF) [2]. Regardless of classification, the management of AF aims at three main objectives: etiological diagnosis, complication prevention, and heart rate (HR) control [2].

Treatment of pAF can be classified into rate- and rhythm-control strategies. Both can improve symptoms, but neither has been conclusively shown to improve survival compared with other [3], with the exception of high-cardiovascular-risk patients who are treated early in the course of their disease, as it was recently shown in EAST AFNET4 trial [4]. Rate control startegy addresses symptoms related to pAF, it is commonly the first step in the management of patients with pAF and other supraventricular tachycardias [5]. Agents used for rate control include non-dihydropyridine calcium channel blockers and non-selective beta-blockers [2,5]. Both types of agents target the atrioventricular node of the cardiac electrical conduction system to hinder the reverberant electrical impulses created in the atrial cardiac tissue during AF [6]. The most common non-dihydropyridine calcium channel blocker and non-selective beta-blocker used in the management of pAF are diltiazem and metoprolol, respectively, with both agents being used interchangeably according to physician preference, patient characteristics and availability. Specific recommendations on the use of one agent vs. the other have not been formally advanced [2,5]. Recently, few retrospective studies [7-11] and a small number of trials [12-16] have compared the use of diltiazem vs. metoprolol for the management of pAF.

Given a lack of formal recommendations on the superiority of either diltiazem or metoprolol for the management of pAF, we performed a meta-analysis of randomized controlled trials comparing the effectiveness of diltiazem or metoprolol for rate control in patients with pAF. We also evaluated secondary outcomes primarily concerned with safety and tolerability.

2. Methods

We conducted a systematic review of the literature on randomized controlled trials comparing the use of diltiazem and metoprolol for the management of pAF. We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [17]. The protocol for the present study was registered in the International Prospective Register of Systematic Reviews (PROSPERO 2019 CRD42019123133).

The Medical Subject Headings (MeSH) terms “diltiazem”, “metoprolol” and “atrial fibrillation” were selected and used for identifying potential studies from EMBASE, PubMed and Cochrane Controlled Register of Trials (CENTRAL). We limited the search periods as follows: 1998 to 2020 for CENTRAL, 2005 to 2020 for MEDLINE, 2005 and 2020 for EMBASE. Search was performed on February 2nd, 2020. Three independent reviewers (C.C., I.W., J.X.) screened the abstracts obtained from the formerly described search strategy for inclusion and exclusion criteria. A fourth reviewer (H.J.) adjudicated the studies for final study inclusion. Studies comparing metoprolol to diltiazem for the management of either pAF or persistent AF were included.

Our primary outcome was achievement of a HR <100 beats per minute or a decrease ≥20% of baseline HR. The literature search periods have been previously described. Only studies published in English, Spanish or Mandarin were included. Studies evaluating AF management during the immediate postoperative period were excluded.

Information extracted from eligible studies included patient characteristics (age and sex), treatment drug, dose and route of administration, HR at different points in time, percentage of patients achieving HR control at different points in time, systolic blood pressure (SBP) at different points in time, adverse events and/or death. The primary outcome was directly extracted from published results. In order to estimate the hazard ratio of HR control, data-sets with time-to-event and event type were reconstructed using previously published methodology [18]. Briefly, hypothetical data sets of survival data were reconstructed

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based on data for individual subjects when available or based on the percentage of patients achieving HR control at different time points. Secondary outcomes were evaluated in terms of absolute mean difference in HR, SBP, and odds ratio of developing adverse events and/or death.

Statistical analysis was performed using R statistical programming language version 3.5.2 (R Foundation for Statistical Computing) [19]. Additional libraries used for this analysis included survival and meta [20,21]. Forest plots for effect measures were created using the meta library. Reconstructed survival data was used to estimate hazard ratios for each study using the survival library, and a forest plot was then performed using the meta library [20,21]. Study quality was evaluated using the Cochrane bias assessment tool [22]. Two reviewers (C.C. & J.X.) assessed bias using the Cochrane bias assessment tool and discrepancies were addressed by a third reviewer (I.W.). Funnel plots were created to graphically assess small-study effects, and Begg and Mazumdar's Rank Correlation Test was used to test the null hypothesis of funnel plot symmetry.

Heterogeneity was measured using Higgins I^2 statistic. Fixed and random effect models were estimated for all the measured effects. A final estimate and confidence interval were selected based on the level of heterogeneity observed, with a random effects model being selected when an I^2 level > 10% was observed.

3. Results

3.1. Study selection

Four hundred and sixty three studies were identified from database searching. After removal of duplicates, 440 studies were screened for eligibility. After review of titles and abstracts, 428 studies were rejected for relevance reasons. Most of these studies were rejected because they were case-control studies or review papers. Twelve papers remained for full text evaluation. Of these 12 studies, Sandberg et al. 2015, Horjen et al. 2016, Ulimoen et al. 2014, and Ulimoen et al. 2014 provided insufficient data. Trials NCT02695992 and NCT02025465 did not have results available. Ulimoen et al. 2013 and Karaca et al. 2007, evaluated persistent AF [15,16]. Finally, trial NCT01914926 was the same as one of the included studies. Thus, a total of three studies were included for the final analysis (Fig. 1).

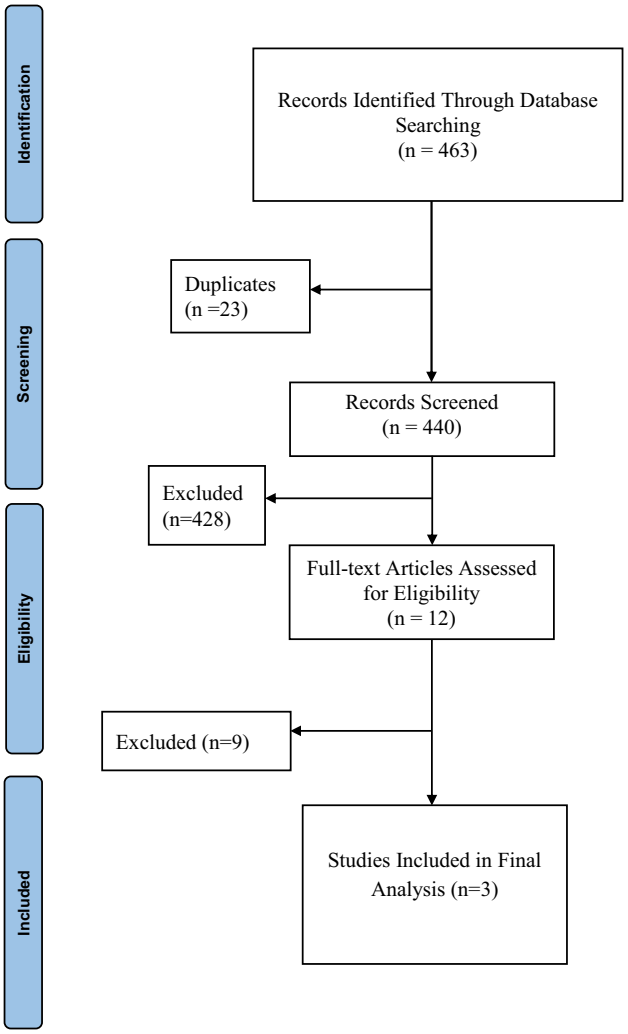

Fig. 1. PRISMA Flowchart.

3.2. Study characteristics

Fromm et al. [12] compared IV diltiazem 0.25 mg/kg (maximum 30 mg) versus IV metoprolol 0.15 mg/kg (maximum 10 mg). Demircan et al. [13] used diltiazem (0.25 mg/Kg IV, maximum dose 25 mg) and metoprolol (0.15 mg/Kg IV, maximum dose 10 mg).

Diao et al. [14] used IV diltiazem 10 mg once (maximum dose 10 mg) and IV metoprolol 5 mg once (maximum dose 5 mg). Inclusion criteria, exclusion criteria and further details of above studies can be found in supplemental material and supplemental table.

3.3. Risk of bias within studies

With exception of the Demircan et al. study, all studies presented with some sort of biases (Fig. 2). The main identified source of bias was not explicitly stating the type of analysis performed, particularly if a per protocol or intention-to-treat analysis was performed. Additionally, Fromm et al. reported incomplete outcome data. Diao et al. did not specify their methods for randomization.

3.4. Results of individual studies

The total number of subjects included in each study were 40, 48 and 52 for Demircan et al., Diao et al., and Fromm et al. respectively. Male vs. female distribution and mean age was similar between treatment groups and studies, as was age distribution. Mean HR at 15 min was lower in the diltiazem group vs. metoprolol group (100 vs. 107.5, 95 vs. 106, and 90.3 vs 115.6 beats per minute for the Demircan et al.,

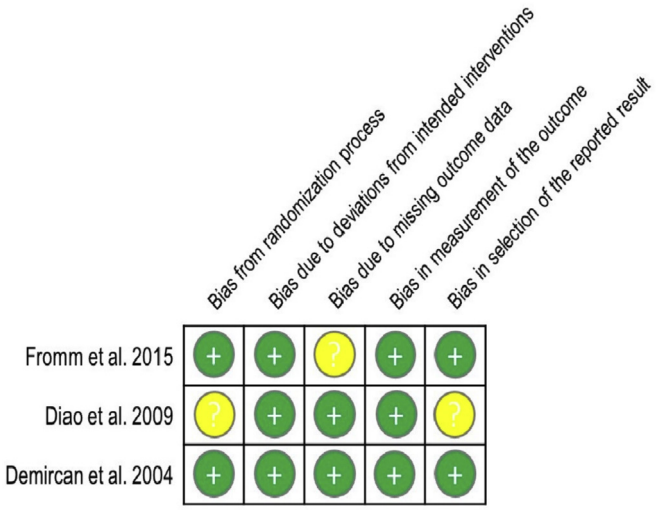

Fig. 2. Summary of Risk of Bias Assessment.

Diao et al., and Fromm et al. studies respectively). Results of included studies are summarized in Table 1.

3.5. Results of meta-analysis

After reconstruction of survival data, hazard ratios were estimated at 4.6 (95% CI: 2.3–9.3), 1.8 (95% CI: 0.92–3.6) and 1.3 (95% CI: 0.68–2.3) for Fromm et al., Demircan et al., and Diao et al. respectively. Although point estimates for all three studies favored diltiazem for the management of pAF, only Fromm et al., reported a confidence interval suggesting strong evidence of faster HR control with diltiazem. When pooled together in a fixed effects model, the results of these studies demonstrated a hazard ratio with a confidence interval strongly favoring diltiazem (HR = 2.05, 95% CI: 1.4–3). A random effects model also favored diltiazem for HR control (HR = 2.14, 95% CI: 1.01–4.54) albeit with weaker statistical evidence. Based on the I^2 statistic (74%), strong evidence of heterogeneity in terms of HR normalization exists across the three studies favoring the use of a random effects model.

Both a fixed effect and a random effects model revealed a strong evidence favoring diltiazem for HR reduction (MD in HR = −18.90 bpm [95% CI: −20.76 to −17.04], −17.24 bpm [95% CI: −19.09 to −15.39] and − 15.05 bpm [95% CI: −16.87 to −13.26] at 5, 10 and 15 min respectively) Fig. 3. Based on the I^2 statistic (0%), no evidence of heterogeneity in terms of mean difference in HR exists across the three studies. Fig. 4 shows weighted kaplan meier curve for HR normalization based on random effects model.

With regards to safety, no differences in SBP at 15 min among the Demircan et al., Diao et al., and Fromm et al. studies were observed in either a fixed nor in a random effects model (MD in SBP at 15 min = 0.04 mmHg [95% CI: 2.89–2.81]). No evidence of heterogeneity was observed for either of these outcomes.

3.6. Risk of bias across studies

Funnel plots for HR mean difference at 5, 10 and 15 min and for HR normalization did not show a strong evidence of asymmetry (Online Appendix). Accordingly, no strong evidence of funnel plot asymmetry was observed after performing Begg and Mazumdar Rank Correlation Tests (*p*-values 0.12, 0.12, 0.6 and 0.6 for HR mean difference at 5, 10, 15 min and HR control respectively).

4. Discussion

We conducted an updated systematic review and a meta-analysis of patients receiving diltiazem or metoprolol for the management of pAF and identified 3 randomized controlled trials comparing the use of diltiazem and metoprolol for the management of pAF [12-14]. Our analysis provided strong statistical evidence of a greater reduction in HR in the immediate period after treatment initiation (5, 10 and 15 min) in the diltiazem groups, and a greater reduction in HR at last measurement with diltiazem. Our analysis also suggested a faster HR normalization with diltiazem treatment in the management of pAF. No differences in SBP were observed between the metoprolol and diltiazem groups.

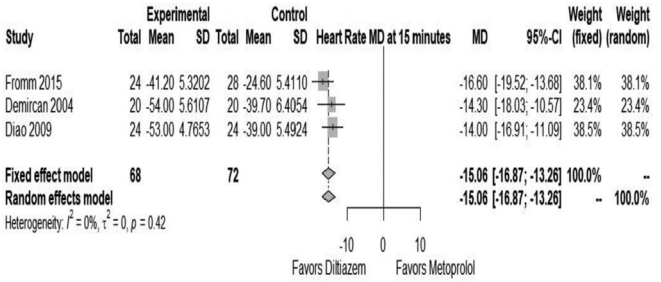

Fig. 3. Mean difference in Heart Rate at 15 min using fixed and random model effects.

Martindale et al. performed a systematic review of randomized controlled trials comparing calcium channel blockers with beta blockers for the management of pAF [23]. In their systematic review Martindale et al. were able to identify the Demircan et al. and Fromm et al. studies, which were the only two studies included in their analysis [12,13,23]. Of note, the study published by Fromm et al. had at that time only been published as an abstract, limiting the data availability of this study for authors of this previous systematic review and meta-analysis [23]. In addition to better data availability on the Fromm et al. study, our study improved on the previous work of Martindale et al. by including the study performed by Diao et al. [14] Given our improved access to data from these three studies, we were able to reconstruct survival data for these three studies to perform a survival analysis on the hazard ratio of HR normalization. This contrasts with the approach of Martindale et al. who estimated the relative risk of achieving HR normalization [23]. Given that the treatment of pAF aims at rapidly achieving HR normalization, by comparing diltiazem vs. metoprolol with a hazard ratio of HR normalization (vs. risk of HR normalization) we expect our analysis to provide better information on how rapidly these agents achieve their intended effect, a measurement that may be of interest to attending clinicians. Our analysis did demonstrate a faster HR normalization with diltiazem that could be considered "significant" in traditional terminology. In addition, our analysis revealed larger differences in HR in the immediate periods after the administration of diltiazem. When pooled together, these findings suggest that diltiazem may be more effective in achieving HR control rapidly in patients with pAF.

In terms of safety, no differences in SBP were identified between the diltiazem and metoprolol group of studies evaluating these drugs for the management of pAF. Given the lack of data availability from the Fromm et al. study, Martindale et al. were not able to assess differences in BP between the groups.

5. Limitations

Limitations of our analysis include a limited number of studies, and suboptimal quality of studies. To the best of our knowledge only one clinical trial comparing diltiazem and metoprolol for the management of pAF is actively recruiting individuals (NCT02025465). We expect that findings from this and other future studies evaluating the use of diltiazem and metoprolol provide further information on the use of these agents in the management of pAF. Of note, survival analysis evaluating

Table 1
Results of selected studies.

Author	Year	Group	Dose	n	Male (%)	Age (m ± sd)	Baseline HR (m ± sd)	HR at 15 min (m ± sd)	Baseline SBP (m ± sd)	SBP at 15 min. (m ± sd)
Fromm	2015	Diltiazem	0.25 mg/Kg	24	47	66.2 ± 13.4	136.8 ± 15.3	90.3 ± 14.4	132.4 ± 23.8	NA
		Metoprolol	0.15 mg/Kg	28	53	69.5 ± 14.8	142.2 ± 16.5	115.6 ± 23	129 ± 19.8	NA
Diao	2009	Diltiazem	10 mg	24	42	57 ± 11	154 ± 17	95 ± 31	136 ± 30	121 ± 21
		Metoprolol	5 mg	24	50	58 ± 12	151 ± 18	106 ± 18	144.0 ± 23	125 ± 18
Demircan	2004	Diltiazem	0.25 mg/Kg	20	40	60.2 ± 13.1	156.4 ± 18	100 ± 14.7	136.5 ± 29.8	121 ± 21.4
		Metoprolol	0.15 mg/Kg	20	50	64 ± 12.9	152 ± 19	107.5 ± 5	143 ± 22.5	124.2 ± 18

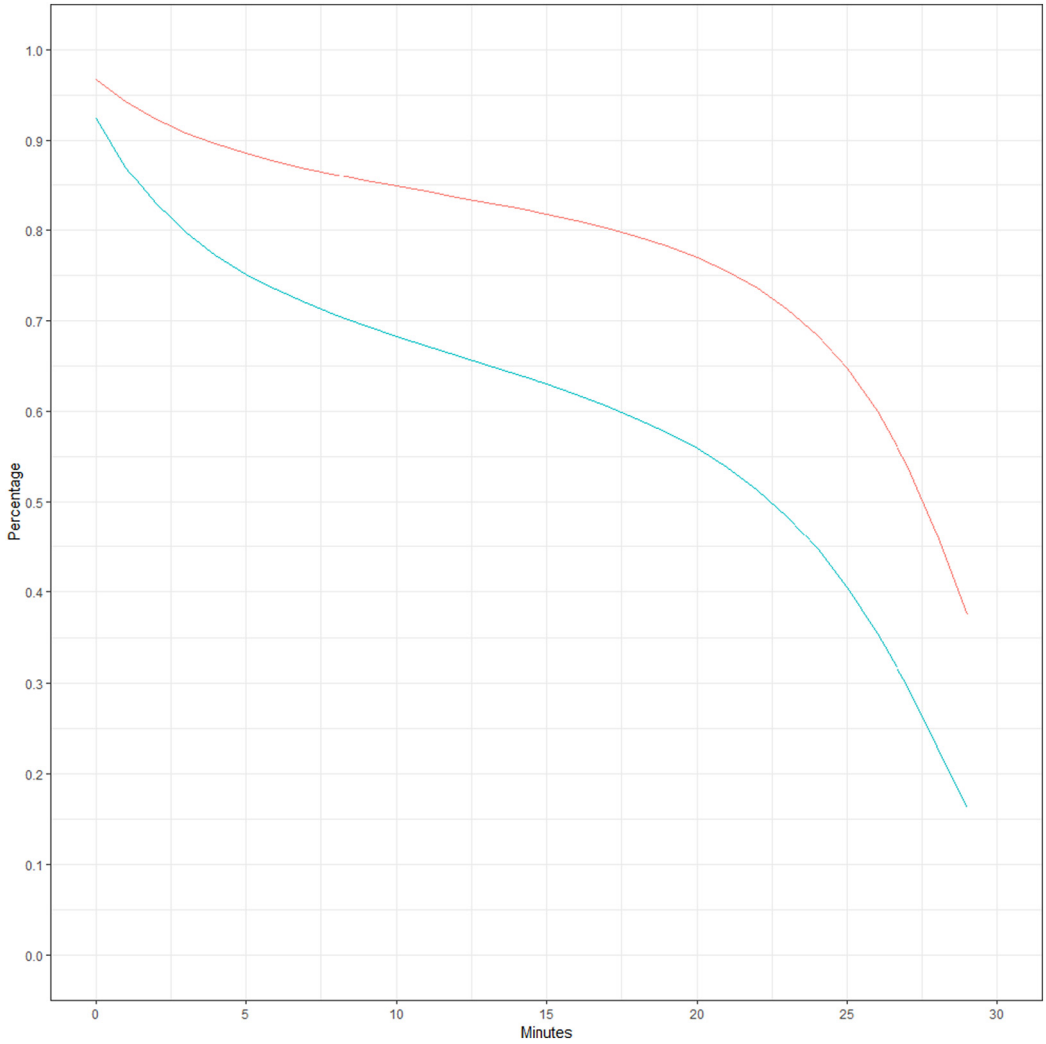

Fig. 4. Weighted Kaplan-Meier Curve for Heart Rate Normalization based on Random Effects Model. Kaplan Meier curve comparing heart rate normalization between the diltiazem groups (blue line) and the metoprolol groups (red line) weighted according to the random effects model.

the hazard ratio of HR normalization will be most useful for the assessment of this outcome in future meta-analyses. The suboptimal quality of the included studies was mainly driven by inconsistencies in the reporting of findings [12,14]. We believe that complete transparency in the reporting of findings and methodology is essential to properly assess studies in a systematic review and meta-analysis. Above results are not applicable to patients with heart failure as those patients were excluded from all 3 trials. Also, diltiazem group achieved faster HR control than metoprolol group with doses used. Two studies used maxiumum dose of diltiazem (30 mg), however metoprolol maxium dose (15 mg) was not used and instead 10 mg was used. We believe that faster HR might be able to achieve if higher metoprolol doses were used. Future trials should use maximum metoprolol doses to compare further effects. We encourage authors of future studies to report results and methodology entirely.

6. Conclusion

In conclusion, when compared to treatment with metoprolol, treatment with diltiazem for pAF resulted in lower HR at 5, 10 and 15 min. Our analysis improves on a previously performed systematic review and meta-analysis by incorporating data from one additional randomized controlled trial, by comparing the safety profile of diltiazem and metoprolol in terms of BP changes, and by incorporating the findings of the analyzed studies into a survival analysis of HR normalization that better reflects the goals of physicians caring for patients with pAF.

Our analysis demonstrated evidence suggestive of a more rapid HR normalization with diltiazem, for which further randomized controlled trials evaluating this outcome may provide further insights.

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Disclosures

Authors deny any relationships with the industry.

Credit author statement

The corresponding author is responsible for ensuring that the descriptions are accurate and agreed by all authors.

Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing - original draft; Writing - review & editing.

Declaration of Competing Interest

We have no relevant conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2021.06.053.

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