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Aldosterone Pathway Blockade to Prevent Atrial Fibrillation: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Despite advances in therapeutic interventions AF remains a progressive and symptomatic disease. Therefore, novel therapeutic interventions targeting the underlying arrhythmogenic substrate for AF is needed. Atrial fibrosis is an important component of the arrhythmogenic substrate of AF and may be initiated by aldosterone binding to the mineralocorticoid receptor. We hypothesized that aldosterone pathway blockade with mineralocorticoid receptor antagonists (MRA) reduces atrial fibrosis, and thus AF.
Methods: We searched OVID MEDLINE, OVID EMBASE and the Cochrane Central Register of Controlled Trials from inception to June 10th, 2016 for randomized controlled trials (RCT) and observational studies addressing MRA and providing information on AF occurrence. Two independent reviewers selected and appraised the data. We performed random-effects meta-analyses. Summary odds ratios (OR) with 95% confidence intervals (CI) were calculated.
Results: We included 14 studies, 5 RCT and 9 observational cohorts, with a cumulative number of 5332 patients (male: 74.9%, age: 65.3 years); 2397 (45.0%) received an MRA (spironolactone or eplerenone). During follow-up, 204 (8.5%) patients treated with MRAs, developed AF, compared to 547 (18.6%) patients, without MRA treatment. Meta-analyses showed a significant overall reduction of AF risk in MRA treated patients (OR: 0.48 CI: 0.38–0.60 $p < 0.001$), including a reduction of new-onset AF (OR: 0.52 CI: 0.37–0.74 $p < 0.001$) and recurrent AF (OR: 0.37 CI: 0.24–0.57 $p < 0.001$), but not post-operative AF (POAF) (OR: 0.60 CI: 0.33–1.09 $p = 0.09$).
Conclusions: MRAs significantly reduce new-onset AF and recurrent AF, but not POAF. MRA treatment can be considered an additive therapeutic strategy in AF.

1. Introduction

Atrial fibrillation (AF) affects 1.5–2% of the European population, and is associated with severe comorbidities. It is associated with a five-fold increased risk of stroke, a three-fold increased incidence of congestive heart failure and a doubled mortality [1]. Despite state-of-the-art therapeutic interventions AF remains a progressive, symptomatic disease. Therefore, novel therapeutic interventions targeting the arrhythmogenic substrate and preventing AF episodes are urgently needed.

The arrhythmogenic substrate of AF is driven by atrial fibrosis [2]. Vice versa, AF itself promotes atrial fibrosis [3].

Cardiac fibrosis formation can be initiated by aldosterone binding to the mineralocorticoid receptor (MR). Aldosterone binding and subsequent cardiac fibrosis formation is indeed associated with increased AF propensity [4].

Studies in dogs have demonstrated that MR antagonists (MRA, spironolactone and eplerenone) can halt the fibrosis formation [5]. Spironolactone down-regulated pro-fibrotic alterations in cardiac fibroblasts and eplerenone suppressed atrial fibrosis formation in dogs [5,6]. In the landmark MRA trials in heart failure patients: RALES, EPHESUS-HF and EMPHASIS-HF, MRAs reduced both morbidity and mortality [7–9]. Moreover, among AF patients undergoing electrical cardioversion, a decrease in aldosterone plasma concentration was associated with longer SR maintenance [10,11]. Therefore, the attributed anti-fibrotic effects of MRAs may be an attractive novel therapeutic AF intervention [5].

In this systematic review and meta-analysis, we investigated the effect of MRAs on new-onset AF, post-operative AF (POAF) or recurrence of AF in a broad patient population with and without heart failure.

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2. Methods

This systematic review was executed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12]. The protocol was registered in the International Prospective Register of Systematic Reviews, registration number: CRD42015026461.

2.1. Search strategy

A medical information specialist (J.L.) systematically searched OVID MEDLINE, OVID EMBASE, The Cochrane Central Register of Controlled Trials and the non-MEDLINE subset of PubMed, from inception to June 10th, 2016. We used both controlled terms (i.e. MeSH-terms in MEDLINE) and free text terms for AF and MRA. Methodological filters were used to identify secondary and primary human studies. No language or date restrictions were applied. We cross-checked the reference lists and the citing articles of the identified relevant studies and adapted the search in case of additional relevant studies (Supplementary data).

2.2. Inclusion and exclusion criteria

We included studies among adults (≥18 years old), addressing the efficacy of MRAs (spironolactone and/or eplerenone), as intervention compared to a control arm, and using AF as outcome. The primary efficacy outcome was the risk of AF during the study-defined follow-up period. (Supplementary data).

2.3. Study selection and critical appraisal

Two reviewers (J.N. and N.v.d.B) selected and appraised title and abstract of all search results with Covidence©, 2015. For all relevant entries the full text paper was reviewed. In case of overlapping data, the study with the largest cohort was included.

The risk of bias in randomized studies was assessed using the Cochrane Collaboration's tool for assessing risk of bias [13]. The quality of non-randomized studies was assessed using the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies [14]. In case of discrepancies with regard to the inclusion of a study or the critical appraisal a third reviewer (J.d.G.) was consulted for consensus.

2.4. Data extraction and analysis

Statistical analyses was performed Comprehensive Meta Analysis© Version 3.3.070, 2014. (Biostat Inc., Englewood NJ, USA). A funnel plot and Egger's test were used to assess publication bias. We used Duval and Tweedie's trim and fill method to adjust for publication bias [13]. We performed sensitivity tests to compare randomized and observational studies. . We considered a p-value of <0.05 or an $I^2 > 40\%$ as a statistical evidence for substantial heterogeneity. Random-effects meta-analyses were performed to adjust for potential statistical heterogeneity. Summary odds ratios (OR) with corresponding 95% confidence intervals (CI) were calculated for dichotomous outcomes.

3. Results

The search identified 1004 unique abstracts. After review of titles and abstracts, 919 were excluded. A total of 29 titles were included based on a review of the abstract. Additionally, two studies of which only the abstract was available were included. After reviewing the full text, we excluded 17 studies (Fig. 1). AF detection was performed by a range of rhythm monitoring modalities, namely: telemonitoring, EKG, Holter and remote monitoring.

3.1. Critical appraisal

We appraised the RCTs overall as low risk of bias. The critical appraisal of the observational cohort studies revealed a high risk of bias, which is due to retrospective collection of the data (Supplementary data).

3.2. Study population

The number of patients ranged between 74 and 1794 patients per study cohort, with 5332 patients in total [15–27]. All study cohorts included both patients with paroxysmal or persistent AF, except for the study cohorts of Ito et al. and Kim et al., who only included patients with persistent AF ($n = 161$ respectively $n = 74$ patients) [19,20]. In the RCTs 1243 (43.2%) patients were randomized to MRAs, whereas in the observational studies 1154 (47.0%) patients received MRAs. This was distributed over 1259 (52.5%) patients treated with spironolactone, and 966 (40.3%) treated with eplerenone. Concomitant treatment was optimal treatment for AF, heart failure and hypertension according to the applicable guidelines or as tolerated by the patient (Table 1). The total study cohort consisted of 74.9% males, and the mean age was 65.3 years. In 4400 patients the outcome was new-onset AF or POAF, whereas in 816 patients the outcome was recurrence of AF. A medical history of heart failure was described in 2866 patients (53.8%); hypertension was present in 3301 patients (61.9%).

3.3. Atrial fibrillation occurrence

During follow-up, 204 (8.5%) patients who were treated with an MRA had an episode of AF, either new-onset or recurrence, compared to 547 (18.6%) patients, who were not treated with an MRA—yielding a RRR of 54.1% and an ARR of 10.1%, resulting in a NNT of 10. Meta-analysis showed a significant reduction of AF risk in MRA treated patients (OR:0.48 CI 95%:0.38–0.60, $p < 0.001$). To correct for potential bias of observational studies, we analyzed the RCTs and observational studies separately. Meta-analysis of RCTs resulted in a significant reduction of AF occurrence (OR:0.59 CI 95%:0.42–0.84, $p = 0.003$). This also applied to the meta-analysis of observational studies (OR: 0.42 CI 95% 0.32–0.55, $p < 0.001$) (Fig. 2). Furthermore, to correct for potential bias of retrospective studies, we analyzed the prospective and retrospective studies separately, which resulted in a similar significant reduction in MRA treated patients both in prospective and retrospective studies, (OR: 0.45 CI 95%: 0.34–0.59, $p < 0.001$) respectively (OR: 0.47 CI 95%: 0.30–0.75:, $p = 0.002$).

3.4. New-onset atrial fibrillation

Subgroup analysis of studies evaluating new-onset AF (1752 patients treated with MRAs and 1753 controls) showed a significant reduction of AF risk in MRA treated patients (OR: 0.52 CI 95%: 0.37–0.74, $p < 0.001$), leading to a RRR of 47.0%. The ARR was 3.2%—yielding a NNT of 31. (Fig. 3) [15,16,26]. The study of Chung et al. included only patients with end-stage renal failure [16]. However, the results of this study did not change the conclusion and exclusion of the study from the analysis yielded a similar significant reduction of AF risk in MRA treated patients (OR: 0.57 CI 95%: 0.38–0.84, $p = 0.005$).

3.5. Recurrence of atrial fibrillation

Among a total of 572 patients with AF at baseline, 210 (36.7%) patients were treated with MRAs. Meta-analysis showed a significant reduction of AF risk in MRA treated patients (OR: 0.37 CI 95%: 0.24–0.57, $p < 0.001$), leading to a RRR of 57.9%. The ARR was 28.1%—yielding a NNT of 4 (Fig. 3) [17,19–21,27].

3.6. Recurrence of atrial fibrillation after an intervention

There was no difference in the AF reduction upon MRA treatment in patients with or without radio frequent catheter ablation [19]. When this study was excluded from the analysis a similar significant reduction of AF risk in MRA treated patients was seen (OR: 0.32 CI 95%: 0.18–0.57, $p < 0.001$). Recurrence of AF after cardioversion was evaluated in three studies [21,23,28]. Meta-analysis showed a significant reduction of AF recurrence after cardioversion in MRA treated patients (OR: 0.30 CI 95%: 0.15–0.57, $p < 0.001$).

3.7. Heart failure and atrial fibrillation risk

Additionally, we evaluated 857 patients with a history of heart failure. Patients in the MRA treatment arm had a significantly lower risk of AF compared to controls (OR: 0.46 CI 95%: 0.34–0.62, $p < 0.001$).

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