# Effects of Mineralocorticoid Receptor Antagonists on Atrial Fibrillation Occurrence: A Systematic Review, Meta-Analysis, and Meta-Regression to Identify Modifying Factors

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***Background*—**Mineralocorticoid receptor antagonists (MRAs) have emerged as potential atrial fibrillation (AF) preventive therapy, but inconsistent results have been reported. We aimed to examine the effects of MRAs on AF occurrence and explore factors that could influence the magnitude of the effect size.

***Methods and Results*—**PubMed, Embase, and Cochrane Central databases were used to search for randomized clinical trials and observational studies addressing the effect of MRAs on AF occurrence from database inception through April 03, 2018. We performed a systematic review and random effects meta-analyses to compute odds ratios with 95% CIs. Meta-regression was then applied to explore the sources of between-study heterogeneity. We included 24 studies, 11 randomized clinical trials and 13 observational cohorts, representing a total number of 7914 patients (median age: 64.2 years; median left ventricular ejection fraction: 49.7%; median follow-up: 12.0 months), 2843 (35.9%) of whom received MRA therapy. Meta-analyses showed a significant overall reduction in AF occurrence in the MRA-treated patients versus the control groups (15.0% versus 32.2%; odds ratio, 0.55; 95% CI, 0.44–0.70 [$P<0.00001$]), with the greatest benefit regarding recurrent AF episodes (odds ratio, 0.42; 95% CI, 0.31–0.59 [$P<0.00001$]) and with significant heterogeneity among the included studies ($I^2=54\%$; $P=0.0008$). Meta-regression analyses showed that effect size was significantly associated with older studies and higher AF occurrence rate in the control groups.

***Conclusions*—**MRAs seem to be effective in AF prevention, especially regarding recurrent AF episodes. **(*J Am Heart Assoc*. 2019;8:e013267. DOI: 10.1161/JAHA.119.013267.)**

**Key Words:** aldosterone, mineralocorticoids • atrial fibrillation • meta-analysis



Atrial fibrillation (AF) is the most prevalent sustained arrhythmia, with an overall estimated prevalence of 1% to 2% among the general population. AF is associated with substantial morbidity, reduced functional status, impeded quality of life, and increased mortality.[1] The pathophysiological mechanisms underlying AF initiation and perpetuation are complex and not completely understood, but evidence indicates that atrial electrical, neurohormonal, and structural remodeling create the substrate for AF development.[1] There is evidence that aldosterone and the activation

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Accompanying Tables S1 through S5 and Figures S1 through S11 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013267

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## Clinical Perspective

### What Is New?

- Mineralocorticoid receptor antagonists may prevent atrial fibrillation (AF), but well-sized randomized trials are lacking.
- This meta-analysis involving 24 studies with 7914 patients, which represents the largest population studied to date, showed a significant overall reduction in AF occurrence in the mineralocorticoid receptor antagonists–treated patients versus the control groups (15.0% versus 32.2%, respectively; odds ratio, 0.55 [95% CI, 0.44–0.70]; $P<0.00001$).
- The greatest benefit was observed in cases of recurrent AF episodes (odds ratio, 0.42; 95% CI, 0.31–0.59 [$P<0.00001$]), especially in populations with high AF occurrence rate.

### What Are the Clinical Implications?

- Our results suggest a clinical benefit of mineralocorticoid receptor antagonists in preventing AF and required well-sized randomized trials to definitively answer the question.

of its receptor, mineralocorticoid receptor, promote cardiac fibrosis and electrical disturbances.[2,3] Mineralocorticoid receptor antagonists (MRAs) have been shown to reduce atrial fibrosis and prevent AF development.[3,4] Primary aldosteronism is strongly associated with the risk for developing AF in both clinical series (odds ratio [OR], 12.1; 95% CI, 3.2–45.2 [$P<0.0001$]).[5] Clinical data have suggested that MRAs could have positive effects on AF burden, but inconsistent results have been reported. Two previous meta-analyses[6,7] investigated the impact of MRAs on AF occurrence but are affected by the noninclusion of nonrandomized clinical trials (RCTs) with the use of restricted search strategies and the absence of any analysis of heterogeneity to investigate modifying factors. Moreover, the benefit of MRAs on AF occurrence in patients who have heart failure (HF) with reduced ejection fraction (HFrEF)[8] was not confirmed in patients without HFrEF or in those without any structural heart disease.

Therefore, we conducted a systematic review of the literature and meta-analysis of both RCTs and observational studies to examine the potential effect of MRA use on AF occurrence using an appropriate strategy to avoid restrictive research (adapted to events considered as secondary end point in studies). We also performed subgroup and meta-regression analyses to explore the source of heterogeneity and identify modifying factors.

## Methods

This systematic review complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Table S1).[9] The protocol was prospectively registered in the International Prospective Register of Systematic Reviews (registration number: CRD42018096969). No ethics committee approval or informed consent was required since this was a retrospective analysis of previously published studies.

### Data Sources and Search Strategy

An extensive, unrestricted, computerized MEDLINE, Embase, and Cochrane Library literature search of articles in English and French was independently conducted by 2 reviewers (J.A., L.D.) according to prespecified selection criteria from inception to April 3, 2018. We also considered studies selected from prior meta-analyses related to the impact of MRAs on AF occurrence[6,7]; trial protocols on trial registry platforms, including clinicaltrials.gov (https://clinicaltrials.gov/), the World Health Organization's International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/), the UK Clinical Trials Gateway (https://www.ukctg.nihr.ac.uk/), and EudraCT (https://eudract.ema.europa.eu/); and data from scientific meeting abstracts and conferences. We used both controlled terms (ie, MeSH terms in MEDLINE) and free-text terms related to MRAs as domain 1 (details of the search are provided in Figure 1). Regarding domain 2 (AF domain), as we did not expect that AF would be reported often in study titles or abstracts (because AF is often a secondary end point of MRA studies), we did not create a specific search domain using the free term "AF" to avoid restricting search strategy. Therefore, we computed a larger domain using the terms "cardiovascular disease" OR "heart disease" OR "atrial fibrillation" (domain 2). The final research was performed as follows: (domain 1) AND (domain 2). Second, a manual search was performed for relevant references from the selected articles.

### Study Selection

Studies evaluating the effects of MRAs (study intervention) compared with non-MRA drugs (placebo or other control drugs, study comparator) on AF occurrence in adult patients were included. Studies using comparators other than drugs were not included. Clinical trials (randomized or nonrandomized, parallel arm, and cluster designs) and clinical observational comparative studies (including retrospective or prospective cohorts and case-control or nested case-control designs) reporting any AF outcomes and the use of MRAs were included. We excluded cross-sectional studies, case series, crossover studies, and case reports. Healthcare/health insurance database studies were also excluded because this type of database does not offer much valuable clinical information to allow the conduct of subgroup and meta-regression analyses.

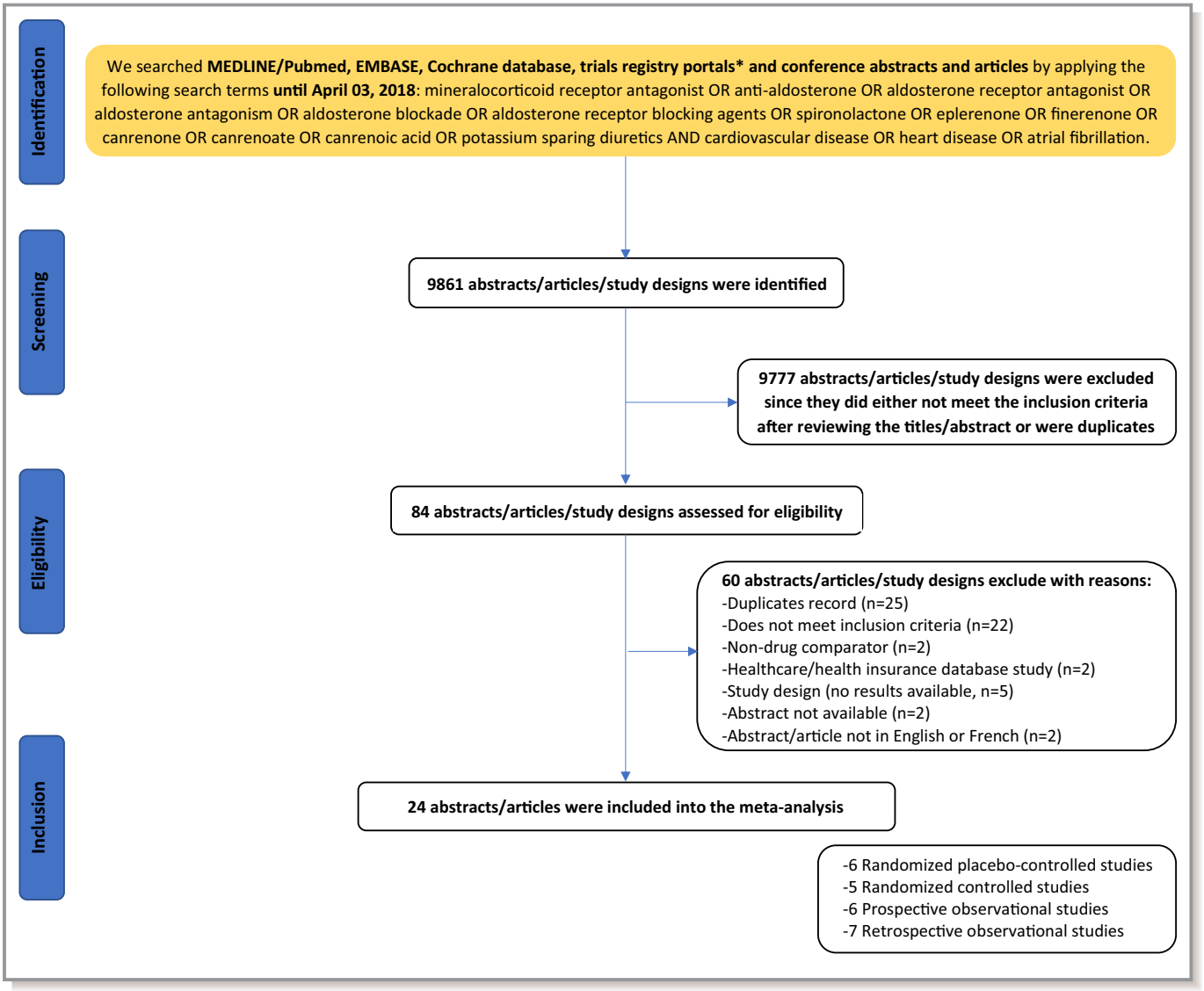


**Figure 1.** Flow diagram of study selection. Clinical trials (randomized, nonrandomized, parallel arm, and cluster designs) and clinical observational comparative studies (including retrospective or prospective cohorts, case-control, or nested case-control designs) were included. *Trials registry portals include clinicaltrials.gov (https://clinicaltrials.gov/), the World Health Organization international clinical trials registry platform (http://apps.who.int/trialsearch/), the UK clinical trials gateway (https://www.ukctg.nihr.ac.uk/), EudraCT (https://eudract.ema.europa.eu/).

## Data Extraction

Two review authors (J.A., L.D.) independently screened study titles and abstracts identified by the search against eligibility criteria. Full reports were obtained for all eligible articles/abstracts. The review authors independently extracted data from the selected studies in duplicate using a standardized data extraction form. Any disagreements were resolved by consensus with senior authors (J.J.P., P.M.). The $\kappa$ statistic revealed excellent agreement between the 2 review authors ($\kappa$=0.86; 95% CI, 0.6–1.0 [$P$<0.0001]). Data extracted included patient demographic and baseline characteristics, patient selection, methodology and study design, inclusion and exclusion criteria, follow-up duration, number of patients, type and dosing of MRAs (when available), and outcomes of interest reported at follow-up. If studies lacked data, corresponding authors were contacted via email to provide the required information. The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Outcome

The primary outcome was the occurrence or recurrence of at least 1 symptomatic or asymptomatic AF, as defined in each study. All types of AF were studied, including postoperative AF (POAF).

## Exploration of Heterogeneity of MRA Effect on AF Occurrence

To explore heterogeneity of MRA effects across trials, we planned to perform prespecified subgroup analyses and univariate meta-regression analyses. The following parameters were considered for the subgroup analyses: study design (placebo and nonplacebo RCTs versus non-RCTs), individual MRA agents used (spironolactone, eplerenone, canrenone, or unspecified MRA), type of AF (eg, new-onset AF, recurrent AF, POAF, cardioversion, and catheter ablation), the presence of HFrEF (defined as patients with left ventricular ejection fraction [LVEF] ≤40% and New York Heart Association class ≥II), quality components including full-text published studies versus scientific meeting abstracts/unpublished studies, and risk of bias (by omitting studies that were judged to be at least at a high or serious risk of bias and industry funding). The following parameters were considered in the meta-regression analyses: clinical status (hypertension, considered as the proportion of patients with hypertension included in each study; patient age, considered as the mean age of the patients in each study; LVEF, considered as the mean LVEF in each study), AF incidence in the control and MRAs groups, and year of publication.

## Risk of Bias (Quality) Assessment

Regarding clinical trials, 2 authors (J.A., L.D.) evaluated risk of bias in individual studies using Cochrane Collaboration's risk of bias tool.[9] Any disagreements were resolved by consensus with senior authors (J.J.P., P.M.). Regarding observational studies, we used the Risk of Bias Tool in Nonrandomized Studies of Interventions (ROBINS-I). After a careful risk of bias assessment for each study, the 2 authors (J.A., L.D.) qualified the studies as "high" or "medium/low" risk of bias. The potential for reporting/publication bias will be further visually explored by funnel plots if ≥10 studies are available for the comparison and with Egger test. We planned to use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group methodology to assess the quality of evidence for all outcomes.

## Statistical Analysis

Statistical analyses were performed with Review Manager version 5.3 (RevMan 5.3, Cochrane Collaboration) and R software for Windows version 3.4.4 (R Foundation for Statistical Computing). Heterogeneity was estimated using $I^2$ statistics and $P$ values for Cochrane heterogeneity tests. Substantial between-study heterogeneity was defined as $I^2$ >50%, and significant heterogeneity was defined if $P$<0.10. We used Mantel-Haenszel summary OR with random effect. Continuous variables were analyzed as the mean difference. For categorical variables, we calculated the OR with 95% CI using the total number of events and patients extracted from the individual studies, with an OR <1 signifying a reduced occurrence of AF in the MRA group. Robustness of the main result was assessed by several sensitivity analyses by excluding: (1) each study sequentially; (2) asymmetric studies on the funnel plot; (3) most influential trials (defined as studies with a weight ≥5.0%); and (4) less influential trials (defined as studies with a sample size <100 patients). Regarding meta-regression analyses, each trial was weighted using inverse variance, and each parameter significantly associated with treatment effect (MRAs versus controls) on AF occurrence was then studied with linear regression analysis between the OR logarithms and quantitative variables. Unweighted logistic regression analysis between the positive status of the trial and quantitative variables was performed. A $P$<0.05 was considered statistically significant.

## Results

The flow chart is presented in Figure 1. The inverted funnel plot for the overall mortality end point did not suggest any substantial publication bias (Figure S1) and the Egger test did not show any significant asymmetry ($P$=0.25).

## Descriptions of Included Studies

Details of the study characteristics are presented in Table. Twenty-four studies enrolled a total of 7914 adult patients, with 2843 patients in the MRAs arms (35.9%) and 5071 patients in the control arms (64.1%). The median age for the entire population was 64.2 (interquartile range, 51.6–68.0) years. The administered MRAs were spironolactone in 62.5%,[10–25] eplerenone in 12.5%,[8,21,26,27] canrenone in 8.3%,[28,29] and nonspecified in 16.7% of the studies (G. Marchetti, et al, unpublished data, 2012).[30,31] Among the 7914 patients, 4831 (61.1%) were included in new-onset AF studies (including 1397 patients in POAF studies), and the remaining 3083 (38.9%) were included in AF recurrence studies (including 408 and 233 patients in electrical cardioversion and catheter ablation studies, respectively). The median LVEF reported in the 24 studies was 49.7% (interquartile range, 26.0–58.5%). Of the 7914 patients, 2839 were patients with HFrEF (35.9%). The median proportion of patients with hypertension was 58.4% (14.6–80%). The median follow-up was 12.0 (interquartile range, 3.0–36.1) months (range: 0.2–49.8 months) in non-POAF trials and 8.0 (interquartile range, 5.5–21) days (range: 5–30 days) in POAF studies.

## AF Occurrence

As shown in Figure 2, compared with the control, MRAs reduced the risk for AF occurrence (15.0% versus 32.2%; OR,

**Table.** Characteristics of the Clinical Trials Included in the Meta-Analysis

| Study | Type of Publication | Sites, Location | Study Design | Patients, No. (% Treated With MRA) | Population | Primary or Secondary AF Prevention | Mean Age, SD | LVEF at Inclusion, % | HTA, No. (%) | AF Occurrence in the Control Group, % | Comparison | Main Outcome | Follow-Up Duration |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Paziaud et al 2003[10] | Full article | France | Retrospective observational study | 96 (21.9) | Consecutive patients referred for electric cardioversion | Recurrence of AF | 64.3 | 58 | 14.6 | 16.0 | Spironolactone+conventional therapy vs conventional therapy | Successful electric cardioversion | NA |
| Gao et al 2007[11] | Full article | China | Randomized placebo-controlled study | 116 (50.0) | Cardiac patients with HF without any AF history | New-onset AF | 55 | 42 | 58 | 41.4 | Spironolactone 20 mg/d vs placebo | New-onset cardiac arrhythmia occurrence | 6 mo |
| Boldt et al 2008[31] | Full article | Germany | Prospective observational study | 148 (27.0) | Consecutive patients with HFrEF referred for electric cardioversion | Recurrence of AF | 67 | 32 | 83 | 35.2 | MRA+conventional therapy vs conventional therapy | Successful electric cardioversion | 12 d |
| Kim et al 2009[12] | Full article | Korea | Prospective observational study | 74 (6.8) | Patients referred for electric cardioversion | Recurrence of AF | 59 | 44.7 | 29 | 69.6 | Spironolactone+conventional therapy vs conventional therapy | AF recurrence | 13 mo |
| Letsas et al 2009[13] | Full article | Germany | Prospective observational study | 72 (8.3) | Patients with paroxysmal and persistent AF who underwent successful PVI | Recurrence of AF | 54.9 | 54.8 | 19 | 39.4 | Spironolactone+conventional therapy vs conventional therapy | AF recurrence | 12.5 mo |
| Brinkley et al 2010[14] | Abstract | United States | Retrospective observational study | 171 (41.5) | Consecutive patients with dual-chamber ICD (primary prevention) without any AF history | New-onset AF | NA | NA | NA | 58.0 | Spironolactone+conventional therapy vs conventional therapy | New-onset AF detected on ICDs | 21 mo |
| Dabrowski et al 2010 (SPIR-AF)[15] | Full article | Poland | Randomized controlled study | 164 (50.0) | Consecutive patients with recurrent AF episodes | Recurrence of AF | 66 | 69 | 73.2 | 80.5 | Spironolactone 25+β-blocker±enalapril vs β-blocker±enalapril | Incidence of symptomatic AF recurrence | 12 mo |
| Disertori et al 2010 (GISSI-AF)[30] | Full article | Italy | Prospective observational study | 1442 (6.4) | Patients with symptomatic paroxysmal or persistent AF | Recurrence of AF | 68 | 55 | 85.4 | 52.4 | Valsartan±MRA and conventional therapy vs valsartan±conventional therapy | AF recurrence | 12 mo |
| Lopes et al 2010[16] | Abstract | Portugal | Prospective observational study | 156 (29.5) | Cardiac patients with HF without any AF history | New-onset AF | 63 | NA | 55.8 | 13.6 | Spironolactone+conventional therapy vs conventional therapy | New-Onset AF occurrence | 43.2 mo |
| Özaydin et al 2010[17] | Full article | Turkey | Prospective observational study | 269 (25.6) | Patients with HF and LVEF ≤50% referred for CABG and/or valve surgery without any AF history | New-onset AF | 59 | 43 | 53.2 | 23.0 | Spironolactone+conventional therapy vs conventional therapy | New-onset POAF incidence | NA |
| Williams et al 2011[24] | Full article | United States | Retrospective observational study | 83 (27.7) | Patients with ICDs with concomitant AF | Recurrence of AF | 71 | 33.1 | 80.4 | 53.3 | Spironolactone+conventional therapy vs conventional therapy | Hospitalization for AF or need for electric cardioversion | 49.8 mo |
| Billota et al 2012[28] | Full article | Italy | Randomized controlled study | 56 (50.0) | Patients with neurocritical care with cerebral edema | New-onset AF | 57 | NA | NA | 7.1 | Canrenone 200 mg/d+mannitol+furosemide vs mannitol+furosemide | Incidence of new cardiac arrhythmia | 8 d |
| (G. Marchetti, et al, unpublished data, 2012) | Abstract | Italy | Randomized controlled study | 90 (50.0) | Patients with HFrEF with an LVEF ≤35% and first documented AF treated by electric cardioversion | Recurrence of AF | 73 | NA | 57.8 | 44.4 | MRA+conventional therapy vs conventional therapy | Progression to permanent AF | 3 mo |
| Pretorius et al 2012[18] | Full article | United States | Randomized placebo-controlled study | 294 (50.0) | Patients with LVEF ≥30% referred for CABG and/or valve surgery without any AF history | New-onset AF | 59 | 57 | 64.5 | 27.2 | Spironolactone 25 mg/d vs placebo | New-onset POAF incidence | 6 d |

Continued

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**Table.** Continued

| Study | Type of Publication | Sites, Location | Study Design | Patients, No. (% Treated With MRA) | Population | Primary or Secondary AF Prevention | Mean Age, SD | LVEF at Inclusion, % | HTA, No. (%) | AF Occurrence in the Control Group, % | Comparison | Main Outcome | Follow-Up Duration |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Swedberg et al 2012 (EMPHASIS-HF)[8] | Full article | Worldwide | Randomized placebo-controlled study, post hoc analysis | 1794 (50.8) | Patients with HFrEF with LVEF ≤35% and NYHA class II without AF history | New-onset AF | 67.9 | 26 | 64.5 | 4.5 | Eplerenone 25 to 50 mg/d vs placebo | Composite of death from cardiovascular causes or hospitalization for HF | 21 mo |
| Tumasyan et al 2012[19] | Abstract | Armenia | Randomized controlled study | 135 (25.2) | Patients with chronic HF with NYHA class III and AF | Recurrence of AF | 61.1 | NA | NA | 67.3 | Spironolactone+conventional therapy vs ramipril or valsartan or aliskiren+conventional therapy | AF rhythm control and adequate control of ventricular response | 12 mo |
| Ito et al 2013[26] | Full article | Japan | Retrospective observational study | 161 (34.2) | Consecutive patients referred for catheter ablation of long-standing persistent AF | Recurrence of AF | 60.5 | 64 | 50 | 60.4 | Eplerenone+conventional therapy vs conventional therapy | AF recurrence after catheter ablation | 24 mo |
| Grigoryan et al 2015[20] | Abstract | Armenia | Randomized placebo-controlled study | 42 (50.0) | Patients with paroxysmal AF with LVEF ≥40% | Recurrence of AF | 51.6 | NA | NA | 28.6 | Spironolactone 25 to 50 mg/d vs placebo | AF recurrence | 8 mo |
| Simopoulos et al 2015[21] | Full article | Greece | Retrospective observational study | 332 (39.8) | Patients with HF and LVEF ≤40% referred for CABG and/or valve surgery without any AF history | New-onset AF | 64.2 | 36 | NA | 45.0 | Spironolactone or eplerenone 25 to 50 mg/d+conventional therapy vs conventional therapy | New-onset POAF incidence | 1 mo |
| Vukicevic et al 2016[22] | Abstract | Serbia | Retrospective observational study | 226 (15.0) | Consecutive patients referred for CABG without any AF history | New-onset AF | 63.9 | NA | NA | 22.4 | Spironolactone+conventional therapy vs conventional therapy | New-onset POAF incidence | 5 d |
| Bosone et al 2017[29] | Full article | Italy | Randomized controlled study | 289 (33.9) | Patients with hypertension and type 2 diabetes mellitus with AF history | Recurrence of AF | 68 | 61 | 100 | 40.8 | Canrenone 10 to 100 mg/d+ramipril 5 mg/d vs amlodipine 5 mg/d or ramipril 5 mg/d+hydrochlorothiazide | AF recurrence | 12 mo |
| Cikes et al 2018 (TOPCAT)[25] | Full article | Worldwide | Randomized placebo-controlled study | 1207 (50.9) | Patients with symptomatic HF and LVEF ≥45% | New-onset AF (n=1005) and recurrence of AF (n=314) | 71 | 60 | NA | 9.3 | Spironolactone 15 to 45 mg/d vs placebo | Composite of cardiovascular mortality, aborted cardiac arrest, or HF hospitalization | 34.8 mo |
| Tsutsui et al 2018 (J-EMPHASIS-HF)[27] | Full article | Japan | Randomized placebo-controlled study | 221 (50.2) | Patients with HFrEF with LVEF ≤35% and NYHA class II without AF history | New-onset AF | 68.7 | 26.1 | 58.4 | 1.8 | Eplerenone 25 to 50 mg/d vs placebo | Composite of death from cardiovascular causes or hospitalization for HF | 29 mo |
| Shavit et al 2018[23] | Data not published in the original study but collected during the investigation[23] | Israel | Prospective observational study | 276 (35.9) | Consecutive patients referred for cardiac surgery without any AF history | New-onset AF | 69 | NA | 80 | 28.8 | Spironolactone 25 mg/d+conventional therapy vs conventional therapy | New-onset POAF incidence | 30 d |

AF indicates atrial fibrillation; CABG, coronary artery bypass graft; HF, heart failure; GISSI-AF, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico–Atrial Fibrillation; HFrEF, heart failure with reduced ejection fraction; HTA, hypertension; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NA, not available; NYHA, New York Heart Association; POAF, postoperative atrial fibrillation; PVI, pulmonary vein isolation; SPIR-AF, Effect of combined spironolactone-β-blocker ± enalapril treatment on occurrence of symptomatic atrial fibrillation episodes in patients with a history of paroxysmal atrial fibrillation; TOPCAT, Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist trial.

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0.55 [95% CI, 0.44–0.70]; $P<0.00001$), with a significant heterogeneity between the included studies ($I^2=54\%$; $P=0.0008$). Prespecified sensitivity analyses were not significantly different from those of the primary analysis (Tables S2 and S3).

## Subgroup and Meta-Regression Analyses

Subgroup analyses based on prespecified parameters were performed (reported in Figures 2 and 3, Figures S2 through S9). The benefit of MRAs for reducing the risks for AF occurrence was consistent considering individual MRA agents, quality components, and presence or not of HFrEF. There was a significant interaction between MRA effect and type of AF (higher effect for AF recurrence versus new-onset AF, $P=0.01$).

On the prespecified univariate meta-regression analyses, 2 variables were found to be statistically associated with the effects of MRAs on AF occurrence (Figure 4). First, the reduction in AF occurrence when receiving MRAs was significantly higher ($P=0.045$) in the "oldest" studies. Second, studies with a higher AF occurrence rate in the control groups were significantly more likely to report a beneficial effect of MRAs on AF occurrence than those with a lower AF occurrence rate ($P=0.023$). The probability of a significant positive MRA impact was associated with a higher AF occurrence rate in the control group ($P=0.03$, Figure S10). These 2 predictors (year of publication and AF occurrence rate in the control group) explained 17% and 21% of the variance, respectively. The association between the year of publication with positive outcome for MRAs in AF was mainly driven by the published full text; when excluding the 7 conference

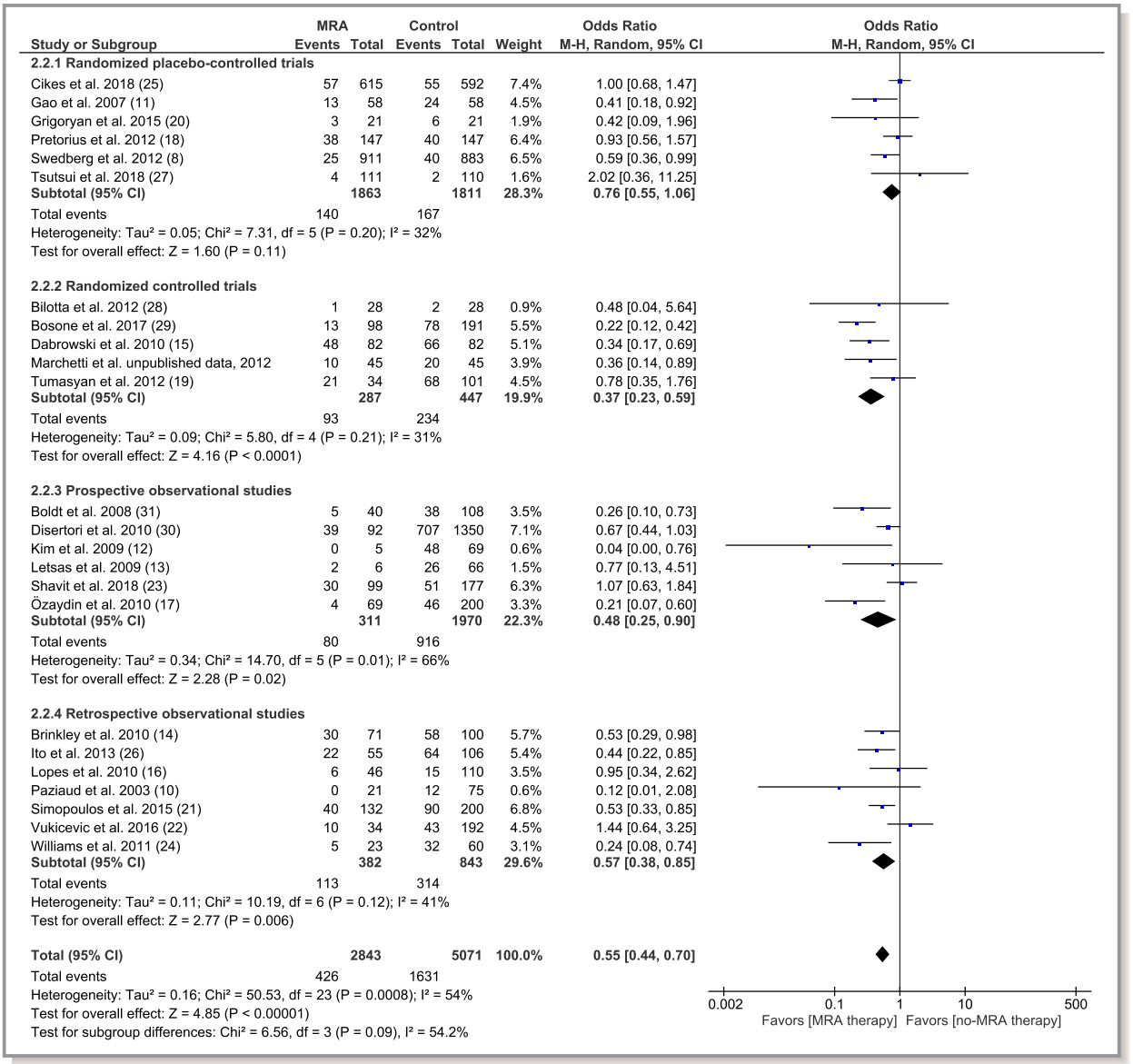


**Figure 2.** Atrial fibrillation occurrence comparing mineralocorticoid receptor antagonist (MRAs) therapy vs controls.

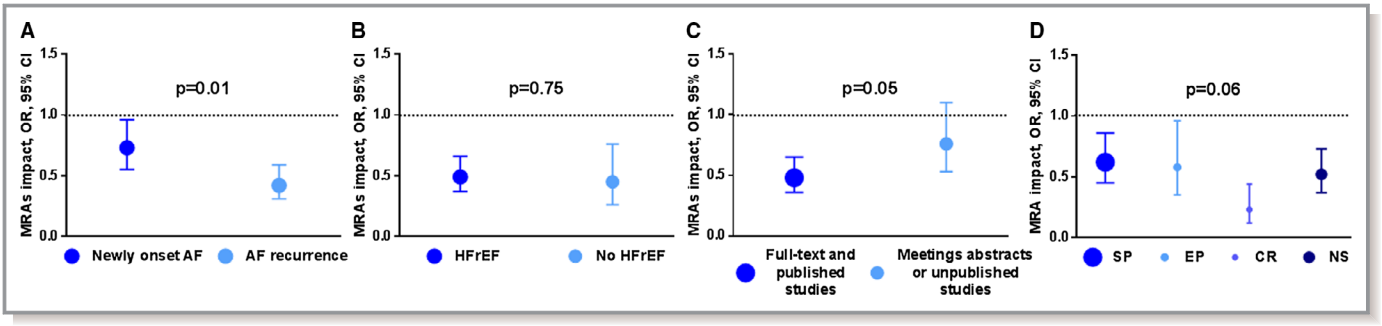


**Figure 3.** Mineralocorticoid receptor antagonist (MRA) benefit in reducing the risk for atrial fibrillation (AF) occurrence in subgroups analyses regarding the type of AF (**A**) (new-onset AF vs AF recurrence), the presence or not of heart failure with reduced ejection fraction (HFrEF) (**B**) (HFrEF, defined as patients with left ventricular ejection fraction [LVEF] ≤40% and New York Heart Association [NYHA] class ≥II), the study status (**C**) (full-text and published studies vs meetings abstracts or unpublished studies), and individual MRA used (**D**). Circle sizes are proportional to trial sample sizes. CR indicates canrenone; EP, eplerenone; NS, nonspecified MRA; OR, odds ratio; SP, spironolactone.

abstracts, the association became nonsignificant (*P*=0.18). The association between AF rate in the control group with positive outcome for MRAs in AF remained consistent with or without the exclusion of conference abstracts. Hypertension, patient age, and LVEF did not significantly influence the effects of MRAs on AF occurrence (*P*=0.82, *P*=0.51, and *P*=0.68, respectively).

## Study Quality and Publication Bias

The quality of included studies is presented in Tables S4 and S5.[32,33] According to the GRADE methodology, our primary outcome had a fair consistency, with moderate to low risk of bias studies, good precision, and no evident publication bias. However, it had substantial heterogeneity. Hence, the quality of evidence was judged to be moderate.

## Discussion

Two previous meta-analyses[6,7] investigated the impact of MRAs on AF occurrence but presented a lack of power caused by insufficient studies included in the meta-analyses, restricted search strategies (with the use of "AF" as a search domain, whereas AF is often not the primary end point of MRA studies and therefore is rarely present in the title and abstract of studies), restricted MRA search strategies (canrenone was not included), and absence of any analysis of heterogeneity to investigate modifying factors. One originality of our search strategy was to include studies considering AF occurrence as a secondary end point to avoid restrictive research. In fact, the main end points of MRA drug studies are generally HF and hypertension. AF is therefore rarely reported in these studies and rarely mentioned in the study title or abstract. Therefore, in our meta-analysis, using "AF" as a search domain would have inevitably caused us to miss some studies that perfectly met our inclusion criteria.

Using this methodology, MRAs were associated with a significantly lower AF risk compared with no MRA treatment (OR, 0.55; 95% CI, 0.44–0.70 [*P*<0.00001]). This effect remained consistent across subgroups with respect to sensitivity and meta-regression analyses. The effect seems to be larger regarding AF recurrence compared with new-onset AF. This may be explained by the antifibrotic effects of MRAs, since fibrosis is present in patients with AF to a greater extent compared with those without AF.[34] Unfortunately, when restricting meta-analysis only to RCT versus placebo subgroup, the efficacy of MRAs did not reach statistical significance (OR, 0.76; 95% CI, 0.55–1.06 [*P*=0.11]). This may be explained by the low AF rate in the control group (9.2%) compared with other types of studies (44.9% when considering RCT, prospective, and retrospective observational studies). Interestingly, the MRA efficacy does not seem confined to patients with HF, as initially suggested by previous meta-analyses[6,7] and in the post hoc analysis of EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure).[8] This trial was the first large and randomized placebo-controlled study to test the hypothesis that MRAs could decrease AF occurrence. In this study, 1794 patients with HFrEF who had LVEF ≤35% and New York Heart Association class II without AF history were enrolled. The median LVEF was 26%. Patients were randomized to receive either eplerenone 25 to 50 mg/d or placebo during a 21-month follow-up period. The primary end point was a composite of death from cardiovascular causes or hospitalization for HF. New-onset AF occurred in 25 of 911 (2.7%) patients in the eplerenone group and 40 of 883 (4.5%) patients in the placebo group (hazard ratio, 0.58; 95% CI, 0.35–0.96 [*P*=0.034]). The beneficial effects of MRAs, independent of the presence of HF, were also recently highlighted in another meta-analysis.[35] This meta-analysis studied the effects of MRAs in patients with ST-segment–elevation myocardial infarction without HF or with a reduced LVEF of

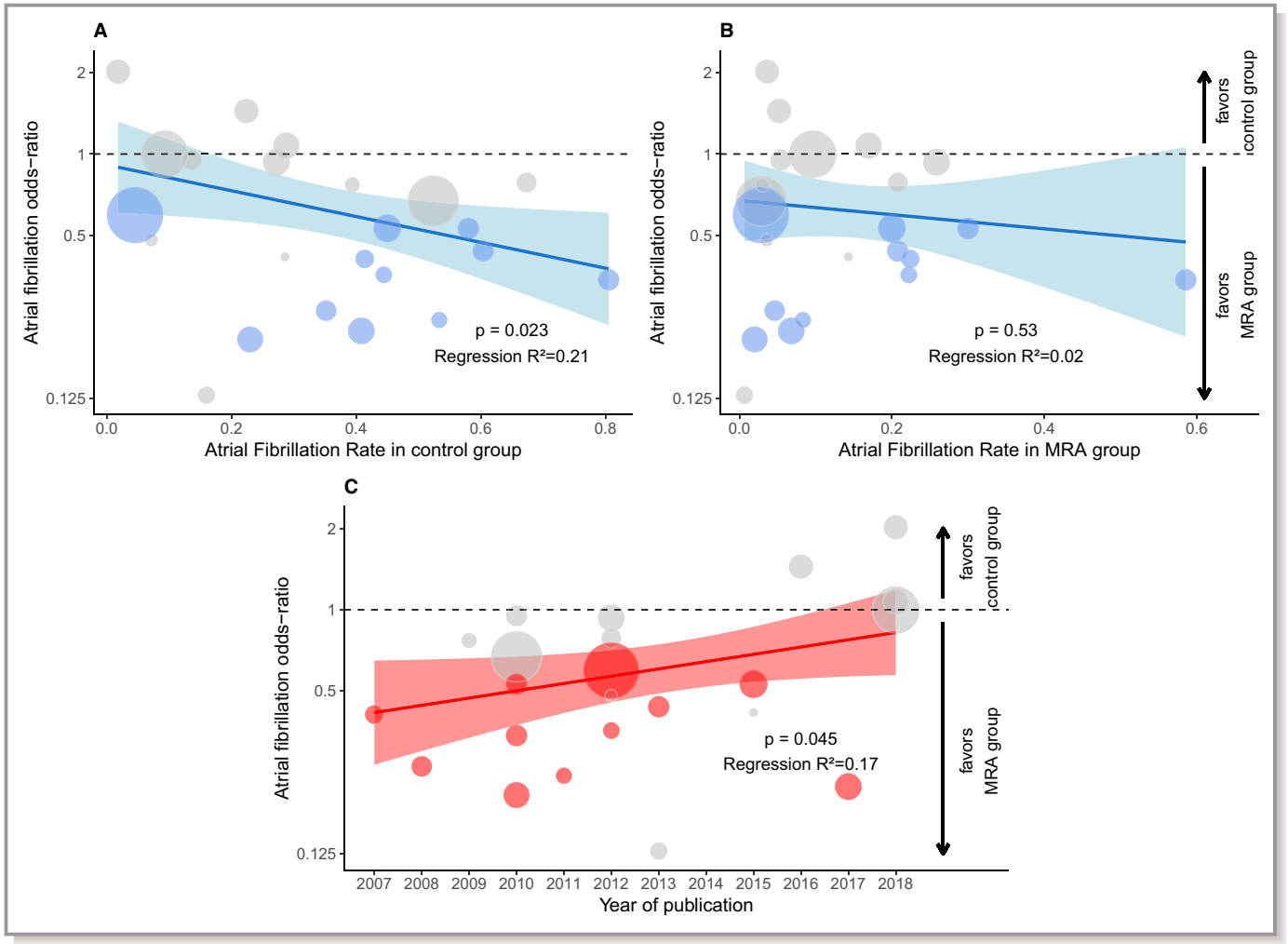


**Figure 4.** Treatment effects (both mineralocorticoid receptor antagonists [MRAs] and controls) on atrial fibrillation (AF) occurrence were associated with a high AF occurrence rate in the control group (**A**) but not with the AF occurrence rate in the MRA group (**B**). Treatment effects (both in the MRA group and controls) on AF occurrence were associated with the year of publication of the study (**C**). Circle sizes are log-proportional to trial sample sizes. Blue (AF occurrence panels) and red (year of publication panel) circles indicate trials with a positive primary outcome effect (AF occurrence, as defined by the trial authors).

<40% (10 RCTs, 4147 patients). MRA treatment decreased mortality (2.4% versus 3.9%; OR, 0.62 [95% CI, 0.42–0.91]; *P*=0.01) compared with the control group. A possible mechanism for MRA impact on AF may pass through the prevention of electrical remodeling and fibrosis.[2–4,36]

MRAs did not significantly reduce the risk of new-onset POAF, but only 1 of the 5 studies included in this analysis was an RCT and we observed a significant heterogeneity across studies included.[18] POAF is a multifactorial phenomenon, and aldosterone might play an important role in POAF development. Experimental studies have shown that aldosterone promotes myocardial inflammation and fibrosis, modulates ionic currents, induces oxidative stress, and enhances cardiac damage during ischemia-reperfusion, particularly by increasing cardiomyocyte apoptosis.[2,4,36,37] All of these phenomena constitute a potential substrate for POAF occurrence. Preliminary findings support this hypothesis, with higher preoperative aldosterone plasma levels in patients with POAF than in those without POAF.[37] The ALDOCURE (Spironolactone and Perioperative Atrial Fibrillation Occurrence in Cardiac Surgery Patients) multicenter double-blind RCT from our group (NCT03551548), specifically designed to test the impact of spironolactone on POAF occurrence after elective coronary artery bypass graft±aortic valve replacement in patients with preserved LVEF, may resolve this issue.

In our meta-analysis, we observed large variations in AF occurrence rates in the control group (Table). We explored the influence of AF rate variations between trials on AF occurrence using prespecified meta-regression analyses (Figure 4). For the 24 trials included, AF occurrence rate ranged between 1.8%[27] and 80.5%[15] (mean: 36.1%). "Positive" MRA trials had a higher occurrence of AF in the control group than "negative" trials.

The probability of a significant positive MRA impact was associated with a higher AF occurrence rate in the control group ($P$=0.03, Figure S10). This finding may indicate that the results of MRA trials in the field of AF are influenced by excessively high AF occurrence rates in control groups. Moreover, we can suppose that MRAs are more effective for patients presenting with frequent AF recurrences at baseline. This hypothesis is supported by the results of the study by Dabrowski et al,[15] in which a spectacular effect of spironolactone on the number of AF episodes during a 12-month follow-up period was reported. In this study, the included patients exhibited at baseline (before randomization) ≈4 episodes during 3 months and a long history of AF (for 4 years). A long history of highly recurrent AF might indicate larger cardiac fibrosis and atrial remodeling and could therefore select patients who can benefit most from MRA therapy. Large trials dedicated to assessing this hypothesis are warranted.

Finally, the year of publication for a study was significantly associated with the study results, with a higher probability of having a positive effect of MRAs in "old" studies compared with "recent" ones. This result may be explained by the constant improvement of therapeutics every year, making it more difficult to demonstrate efficiency. This may be likely in the setting of AF with the advent of catheter ablation and the common use of antiarrhythmic drugs such as amiodarone.

## Study Limitations

A potential limitation of our meta-analysis is the inclusion of nonrandomized studies and meeting abstracts. However, this methodology allows us to perform a systematic review and to limit the risk of publication bias. The studies acquired different cohorts and included different MRA agents, different types of AF, and different clinical contexts (POAF studies with short follow-up versus no-POAF studies with longer follow-up), which led to a moderate heterogeneity according to the GRADE score ($I^2$=54% regarding the principal analysis). We explored most of these factors with subgroup and meta-regression analyses, but the absence of individual data clearly limited our ability to address within-study heterogeneity. We decided a priori to use a random effect model because we had concerns of heterogeneity, and because the choice between the 2 models should not be based solely on the observed significant test for heterogeneity. Figure S11 showed AF occurrence comparing MRA therapy versus controls using a fixed effect model and did not exhibit any significant difference with the random one. The absence of individual data prevented us from highlighting, for example, potential differences in the efficacy among MRA agents, especially in patients with diabetes mellitus where studies suggested that spironolactone increased glycated hemoglobin and cortisol levels and did not improve endothelial function, whereas eplerenone did. Furthermore, the methods for detecting AF during follow-up are heterogeneous across studies. This is inherent to AF detection and may lead to an underestimation of the AF risk.

## Conclusions

Results from our meta-analysis suggest a substantial efficacy of MRAs in reducing the risk of AF in patients with or without HF, especially in the setting of AF recurrence prevention. These findings support the hypothesis of mineralocorticoid receptor inhibition as an emerging treatment option for the prevention of AF, particularly in patients with "active" AF with frequent episodes. Future adequately powered randomized studies are required to assess such a hypothesis.

## Acknowledgments

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## Disclosures

None.

## References

1. Andrade J, Khairy P, Dobrev D, Nattel S. The clinical profile and pathophysiology of atrial fibrillation: relationships among clinical features, epidemiology, and mechanisms. *Circ Res*. 2014;114:1453–1468.
2. Salem JE, Alexandre J, Bachelot A, Funck-Brentano C. Influence of steroid hormones on ventricular repolarization. *Pharmacol Ther*. 2016;167:38–47.
3. Reil JC, Hohl M, Selejan S, Lipp P, Drautz F, Kazakow A, Münz BM, Müller P, Steendijk P, Reil GH, Allessie MA, Böhm M, Neuberger HR. Aldosterone promotes atrial fibrillation. *Eur Heart J*. 2012;33:2098–2108.
4. Milliez P, Deangelis N, Rucker-Martin C, Leenhardt A, Vicaut E, Robidel E, Beaufils P, Delcayre C, Hatem SN. Spironolactone reduces fibrosis of dilated atria during heart failure in rats with myocardial infarction. *Eur Heart J*. 2005;26:2193–2199.
5. Milliez P, Girerd X, Plouin PF, Blacher J, Safar ME, Mourad JJ. Evidence for an increased rate of cardiovascular events in patients with primary aldosteronism. *J Am Coll Cardiol*. 2005;45:1243–1248.
6. Neefs J, van den Berg NW, Limpens J, Berger WR, Boekholdt SM, Sanders P, de Groot JR. Aldosterone pathway blockade to prevent atrial fibrillation: a systematic review and meta-analysis. *Int J Cardiol*. 2017;231:155–161.

7. Liu T, Korantzopoulos P, Shao Q, Zhang Z, Letsas KP, Li G. Mineralocorticoid receptor antagonists and atrial fibrillation: a meta-analysis. *Europace*. 2016;18:672–678.
8. Swedberg K, Zannad F, McMurray JJV, Krum H, Veldhuisen DJ VAN, Shi H, Vincent J, Pitt B; EMPHASIS-HF Study Investigators. Eplerenone and atrial fibrillation in mild systolic heart failure: results from the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure) study. *J Am Coll Cardiol*. 2012;59:1598–1603.
9. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA; PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ*. 2015;350:g7647.
10. Paziaud O, Piot O, Rousseau J, Copie X, Lavergne T, Guize L, Le Heuzey JY. External electrical cardioversion of atrial arrhythmia: predictive criteria of success. *Ann Cardiol Angeiol (Paris)*. 2003;52:232–238.
11. Gao X, Peng L, Adhikari CM, Lin J, Zuo Z. Spironolactone reduced arrhythmia and maintained magnesium homeostasis in patients with congestive heart failure. *J Card Fail*. 2007;13:170–177.
12. Kim SK, Pak HN, Park JH, Ko KJ, Lee JS, Choi JI, Kim YH. Clinical and serological predictors for the recurrence of atrial fibrillation after electrical cardioversion. *Europace*. 2009;11:1632–1638.
13. Letsas KP, Weber R, Bürkle G, Mihas CC, Minners J, Kalusche D, Arentz T. Pre-ablative predictors of atrial fibrillation recurrence following pulmonary vein isolation: the potential role of inflammation. *Europace*. 2009;11:158–163.
14. Brinkley D, Chen J. Poster PO4-12: effect of spironolactone on atrial fibrillation in patients with heart failure. *Heart Rhythm*. 2010;7:S262.
15. Dabrowski R, Borowiec A, Smolis-Bak E, Kowalik I, Sosnowski C, Kraska A, Kazimierska B, Wozniak J, Zareba W, Szwed H. Effect of combined spirono-lactone-β-blocker ± enalapril treatment on occurrence of symptomatic atrial fibrillation episodes in patients with a history of paroxysmal atrial fibrillation (SPIR-AF study). *Am J Cardiol*. 2010;106:1609–1614.
16. Lopes R, Lourenco P, Paulo C, Sousa A, Lebreiro A, Mascarenhas J, Silva S, Santos M, Silva H, Bettencourt P. Is there a role for spironolactone in atrial fibrillation prevention? *European Journal of Heart Failure Supplements*. 2010;9:S145.
17. Ozaydin M, Varol E, Türker Y, Peker O, Erdoğan D, Doğan A, Ibrişim E. Association between renin-angiotensin-aldosterone system blockers and postoperative atrial fibrillation in patients with mild and moderate left ventricular dysfunction. *Anadolu Kardiyol Derg*. 2010;10:137–142.
18. Pretorius M, Murray KT, Yu C, Byrne JG, Billings FT, Petracek MR, Greelish JP, Hoff SJ, Ball SK, Mishra V, Body SC, Brown NJ. Angiotensin-converting enzyme inhibition or mineralocorticoid receptor blockade do not affect prevalence of atrial fibrillation in patients undergoing cardiac surgery. *Crit Care Med*. 2012;40:2805–2812.
19. Tumasyan L, Adamyan K, Chilingaryan A. Poster 853: comparative efficacy of renin-angiotensin system modulators on sinus rhythm restoration in chronic heart failure patients with atrial fibrillation. *Eur Heart J Cardiovasc Imaging*. 2012;13:i143–i165.
20. Grigoryan S, Hazarapetyan L. Acute Cardiovascular Care 2015—P 224 The impact of spirolactone therapy on recurrence and atrial structural remodeling in patients with paroxysmal atrial fibrillation. *Eur Heart J Acute Cardiovasc Care*. 2015;4:89.
21. Simopoulos V, Tagarakis G, Hatziefthimiou A, Skoularigis I, Triposkiadis F, Trantou V, Tsilimingas N, Aidonidis I. Effectiveness of aldosterone antagonists for preventing atrial fibrillation after cardiac surgery in patients with systolic heart failure: a retrospective study. *Clin Res Cardiol*. 2015;104:31–37.
22. Vukicevic MV, Putnik S, Potpara TS. GW27-e0978 The relationship between preoperative pharmacotherapy and incident postoperative atrial fibrillation in patients undergoing isolated coronary artery bypass grafting. *J Am Coll Cardiol*. 2018;68:C120.
23. Shavit L, Silberman S, Tauber R, Merin O, Bitran D, Fink D. Preoperative aldosterone receptor blockade and outcomes of cardiac surgery in patients with chronic kidney disease. *Clin Nephrol*. 2018;89:187–195.
24. Williams RS, deLemos JA, Dimas V, Reisch J, Hill JA, Naseem RH. Effect of spironolactone on patients with atrial fibrillation and structural heart disease. *Clin Cardiol*. 2011;34:415–419.
25. Cikes M, Claggett B, Shah AM, Desai AS, Lewis EF, Shah SJ, Anand IS, O'Meara E, Rouleau JL, Sweitzer NK, Fang JC, Saksena S, Pitt B, Pfeffer MA, Solomon SD. Atrial fibrillation in heart failure with preserved ejection fraction: the TOPCAT trial. *JACC Heart Fail*. 2018;6:689–697.
26. Ito Y, Yamasaki H, Naruse Y, Yoshida K, Kaneshiro T, Murakoshi N, Igarashi M, Kuroki K, Machino T, Xu D, Kunugita F, Sekiguchi Y, Sato A, Tada H, Aonuma K. Effect of eplerenone on maintenance of sinus rhythm after catheter ablation in patients with long-standing persistent atrial fibrillation. *Am J Cardiol*. 2013;111:1012–1018.
27. Tsutsui H, Ito H, Kitakaze M, Komuro I, Murohara T, Izumi T, Sunagawa K, Yasumura Y, Yano M, Yamamoto K, Yoshikawa T, Tsutamoto T, Zhang J, Okayama A, Ichikawa Y, Kanmuri K, Matsuzaki M; J-EMPHASIS-HF Study Group. Double-blind, randomized, placebo-controlled trial evaluating the efficacy and safety of Eplerenone in Japanese patients with chronic heart failure (J-EMPHASIS-HF). *Circ J*. 2017;82:148–158.
28. Bilotta F, Giovannini F, Aghilone F, Stazi E, Titi L, Zeppa IO, Rosa G. Potassium sparing diuretics as adjunct to mannitol therapy in neurocritical care patients with cerebral edema: effects on potassium homeostasis and cardiac arrhythmias. *Neurocrit Care*. 2012;16:280–285.
29. Bosone D, Costa A, Ghiotto N, Ramusino MC, Zoppi A, D'Angelo A, Fogari R. Effect of ramipril/hydrochlorothiazide and ramipril/canrenone combination on atrial fibrillation recurrence in hypertensive type 2 diabetic patients with and without cardiac autonomic neuropathy. *Arch Med Sci*. 2017;13:550–557.
30. Disertori M, Lombardi F, Barlera S, Latini R, Maggioni AP, Zeni P, Di Pasquale G, Cosmi F, Franzosi MG; GISSI-AF Investigators. Clinical predictors of atrial fibrillation recurrence in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Atrial Fibrillation (GISSI-AF) trial. *Am Heart J*. 2010;159:857–863.
31. Boldt LH, Rolf S, Huemer M, Parwani AS, Luft FC, Dietz R, Haverkamp W. Optimal heart failure therapy and successful cardioversion in heart failure patients with atrial fibrillation. *Am Heart J*. 2008;155:890–895.
32. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
33. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, Carpenter JR, Chan AW, Churchill R, Deeks JJ, Hróbjartsson A, Kirkham J, Jüni P, Loke YK, Pigott TD, Ramsay CR, Regidor D, Rothstein HR, Sandhu L, Santaguida PL, Schünemann HJ, Shea B, Shrier I, Tugwell P, Turner L, Valentine JC, Waddington H, Waters E, Wells GA, Whiting PF, Higgins JP. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355:i4919.
34. Dzeshka MS, Lip GY, Snezhitskiy V, Shantsila E. Cardiac fibrosis in patients with atrial fibrillation: mechanisms and clinical implications. *J Am Coll Cardiol*. 2015;66:943–959.
35. Dahal K, Hendrani A, Sharma SP, Singireddy S, Mina G, Reddy P, Dominic P, Modi K. Aldosterone antagonist therapy and mortality in patients with ST-segment elevation myocardial infarction without heart failure: a systematic review and meta-analysis. *JAMA Intern Med*. 2018;178:913–920.
36. Alexandre J, Beygui F, Puddu PE, Manrique A, Rouet R, Milliez P. Electrophysiological and antiarrhythmic properties of potassium canrenoate during myocardial ischemia-reperfusion. *J Cardiovasc Pharmacol Ther*. 2015;20:313–321.
37. Alexandre J, Saloux E, Chequel M, Allouche S, Ollitrault P, Plane AF, Legallois D, Fischer MO, Saplacan V, Buklas D, Labombarda F, Blanchart K, Salem JE, Nowoczyn M, Puddu PE, Manrique A, Parienti JJ, Milliez P. Preoperative plasma aldosterone and the risk of atrial fibrillation after coronary artery bypass surgery: a prospective cohort study. *J Hypertens*. 2016;34:2449–2457.

# Supplemental Material

**Table S1**. **PRISMA checklist for the meta-analysis.**

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported section (top-level heading) |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | **Both, title, abstract** |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | **Abstract** |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | **Introduction** |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | **Introduction** |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | **CRD42018096969** |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | **Data Sources and Search strategy, Study selection** |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | **Search strategy, Study selection** |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | **Data Sources and Search strategy, Suppl Table** |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | **Data Sources and Search strategy, Study selection** |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | **Data extraction** |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | **NA** |

# PRISMA 2009 Checklist

| | | | |
|---|---|---|---|
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | **Risk of bias (quality) assessment** |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | **Statistical analysis** |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | **Statistical analysis** |



| Section/topic | # | Checklist item | Reported section # (top-level heading) |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | **Risk of bias (quality) assessment** |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | **Statistical analysis** |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | **Descriptions of Included Studies, flow chart (Fig.1)** |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | **Descriptions of Included Studies, Table 1** |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | **Study Quality and Publication Bias, Suppl tables** |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | **AF occurrence, Subgroup and meta-regression analyses, Figures 2 and 3, Suppl figures** |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | **AF occurrence, Subgroup and meta-regression analyses,** |

# PRISMA 2009 Checklist

| | | | |
|---|---|---|---|
| | | | **Figure 2 and 3, Suppl figures** |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | **Study Quality and Publication Bias, Suppl figures and tables** |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | **Subgroup and meta-regression analyses, Figure 4, Suppl figures and tables** |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | **Discussion** |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | **Discussion** |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | **Conclusion** |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | **Funding** |



*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

**Table S2. Sensitivity analyses to evaluate the contribution of each study to the pooled estimation by excluding each of the studies one after the others.**

| Study | Atrial fibrillation odds-ratio with 95% confidence interval (CI) after removing the study | Weight of the study removed (%) |
|---|---|---|
| **Paziaud et al.2003**[1] | 0.56, 95% CI 0.44-0.71 | 0.6 |
| **Gao et al. 2007**[2] | 0.56, 95% CI 0.44-0.72 | 4.5 |
| **Boldt et al.2008**[3] | 0.57, 95% CI 0.45-0.72 | 3.5 |
| **Kim et al. 2009**[4] | 0.56, 95% CI 0.45-0.71 | 0.6 |
| **Letsas et al.2009**[5] | 0.55, 95% CI 0.43-0.70 | 1.5 |
| **Brinkley et al. 2010**[6] | 0.55, 95% CI 0.43-0.71 | 5.7 |
| **Dabrowski et al. 2010 (SPIR-AF)**[7] | 0.57, 95% CI 0.45-0.73 | 5.1 |
| **Disertori et al. 2010 (GIFFI-AF)**[8] | 0.54, 95% CI 0.42-0.70 | 7.1 |
| **Lopes et al.2010**[9] | 0.54, 95% CI 0.42-0.69 | 3.5 |
| **Özaydin et al. 2010**[10] | 0.57, 95% CI 0.45-0.73 | 3.3 |
| **Williams et al. 2011**[11] | 0.57, 95% CI 0.45-0.72 | 3.1 |
| **Billota et al. 2012**[12] | 0.55, 95% CI 0.43-0.71 | 0.9 |
| **Marchetti et al. 2012**[13] | 0.56, 95% CI 0.44-0.72 | 3.9 |
| **Pretorius et al. 2012**[14] | 0.53, 95% CI 0.42-0.68 | 6.4 |
| **Swedberg et al. 2012 (EMPHASIS-AF)**[15] | 0.55, 95% CI 0.42-0.71 | 6.5 |
| **Tumasyan et al. 2012**[16] | 0.54, 95% CI 0.42-0.70 | 4.5 |
| **Ito et al. 2013**[17] | 0.56, 95% CI 0.44-0.72 | 5.4 |
| **Grigoryan et al. 2015**[18] | 0.56, 95% CI 0.44-0.71 | 1.9 |
| **Simopoulos et al. 2015**[19] | 0.55, 95% CI 0.43-0.71 | 6.8 |
| **Vukicevic et al. 2016**[20] | 0.53, 95% CI 0.42-0.67 | 4.5 |
| **Bosone et al. 2017**[21] | 0.59, 95% CI 0.47-0.74 | 5.5 |
| **Cikes et al. 2018 (TOPCAT)**[22] | 0.53, 95% CI 0.42-0.67 | 7.4 |
| **Tsutsui et al. 2018 (J-EMPHASIS-HF)**[23] | 0.54, 95% CI 0.43-0.69 | 1.6 |
| **Shavit et al.2018**[24] | 0.53, 95% CI 0.42-0.68 | 6.3 |

Asymmetric studies on the funnel plot indicate the largest and smallest trials.

**Table S3. Sensitivity analyses to evaluate the contribution of asymmetric studies on the Funnel plot, of biggest trials (which had a weight percentage ≥5.0%) and of smaller trials (which had sample size <100 patients) to the pooled estimation.**

| Sensitivity analyses | Atrial fibrillation odds-ratio with 95% confidence interval (CI) after removing studies | Weight of the studies removed (%) |
|---|---|---|
| **Removing of asymmetric studies on the Funnel plot**[1,4,5,12,18,23] | 0.56, 95% CI 0.43-0.73 | 7.7 |
| **Removing of largest trials (which had a weight percentage ≥5.0%)**[6,7,8,14,15,17,19,21,22,24] | 0.49, 95% CI 0.32-0.75 | 62.2 |
| **Removing of smallest trials (which had sample size <100 patients)** [1,4,5,11,12,13,18] | 0.61, 95% CI 0.46-0.80 | 17.9 |

**Table S4. Risk of bias in randomized studies, based on the Cochrane Risk of Bias Tool for Randomized Controlled Trials.**

| Study | Random sequence generation | Allocation concealment | Selective outcome reporting | Other bias | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data |
|---|---|---|---|---|---|---|---|
| Billota et al. 2012[12] | Unclear risk | Unclear risk | High risk | High risk | High risk | High risk | Unclear risk |
| Bosone et al. 2017[21] | Unclear risk | High risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| Dabrowski et al. 2010[7] | Unclear risk | Unclear risk | Low risk | Low risk | High risk | Unclear risk | Low risk |
| Gao et al. 2007[2] | Unclear risk | Unclear risk | Low risk | Low risk | Low risk | Unclear risk | Low risk |
| Grigoryan et al. 2015[18] | Unclear risk | Unclear risk | High risk | Unclear risk | Low risk | Unclear risk | Low risk |
| Marchetti et al. 2012[13] | Unclear risk | Unclear risk | High risk | Unclear risk | High risk | High risk | Unclear risk |
| Cikes et al. 2018[22] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| Pretorius et al. 2012[14] | Low risk | Low risk | Low risk | High risk | Low risk | Low risk | Low risk |
| Swedberg et al. 2012[15] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| Tsutsui et al. 2018[23] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| Tumasyan et al. 2012[16] | Unclear risk | Unclear risk | High risk | Unclear risk | High risk | High risk | Unclear risk |

High risk
Low risk
Unclear risk

**Table S5. Risk of bias in observational studies, based on The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool (version 19 September 2016 for cohort-type studies).**

| Study | Bias due to confounding | Bias in selection of participant | Bias in classification of interventions | Bias due to deviations from intended interventions | Bias due to missing data | Bias in measurement of outcomes | Bias in selection of the reported result | Overall bias |
|---|---|---|---|---|---|---|---|---|
| **Boldt et al. 2008[3]** | Low risk | Moderate risk | Moderate risk | Moderate risk | Low risk | Low risk | Low risk | Low risk |
| **Brinkley et al. 2010[6]** | Moderate risk | Moderate risk | Low risk | Low risk | Not interpretable | Low risk | Low risk | Low risk |
| **Disertori et al. 2010[8]** | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| **Ito et al. 2013[17]** | Low risk | Low risk | Low risk | Moderate risk | Low risk | Low risk | Low risk | Low risk |
| **Kim et al. 2009[4]** | Low risk | Moderate risk | Moderate risk | Serious risk | Low risk | Low risk | Low risk | Low risk |
| **Letsas et al. 2009[5]** | Moderate risk | Low risk | Serious risk | Serious risk | Low risk | Low risk | Low risk | Low risk |
| **Lopes et al. 2010[9]** | Moderate risk | Moderate risk | Moderate risk | Serious risk | Not interpretable | Serious risk | Low risk | Moderate risk |
| **Özaydin et al. 2010[10]** | Low risk | Moderate risk | Low risk | Serious risk | Low risk | Low risk | Low risk | Low risk |
| **Paziaud et al. 2003[1]** | Moderate risk | Moderate risk | Serious risk | Serious risk | Moderate risk | Low risk | Low risk | Low risk |
| **Shavit et al. 2018[24]** | Low risk | Moderate risk | Low risk | Serious risk | Low risk | Moderate risk | Low risk | Low risk |
| **Simopoulos et al. 2015[19]** | Moderate risk | Moderate risk | Moderate risk | Serious risk | Moderate risk | Low risk | Low risk | Low risk |
| **Vukicevic et al. 2016[20]** | Moderate risk | Moderate risk | Moderate risk | Serious risk | Not interpretable | Low risk | Low risk | Low risk |
| **Williams et al. 2011[11]** | Moderate risk | Moderate risk | Moderate risk | Serious risk | Moderate risk | Low risk | Low risk | Moderate risk |

Critical risk
Serious risk
Moderate risk
Low risk
Not interpretable

**Figure S1. Funnel plot of standard error (log odds ratio) by odds ratio to evaluate publication bias for effect of MRAs on reducing atrial fibrillation occurrence.**

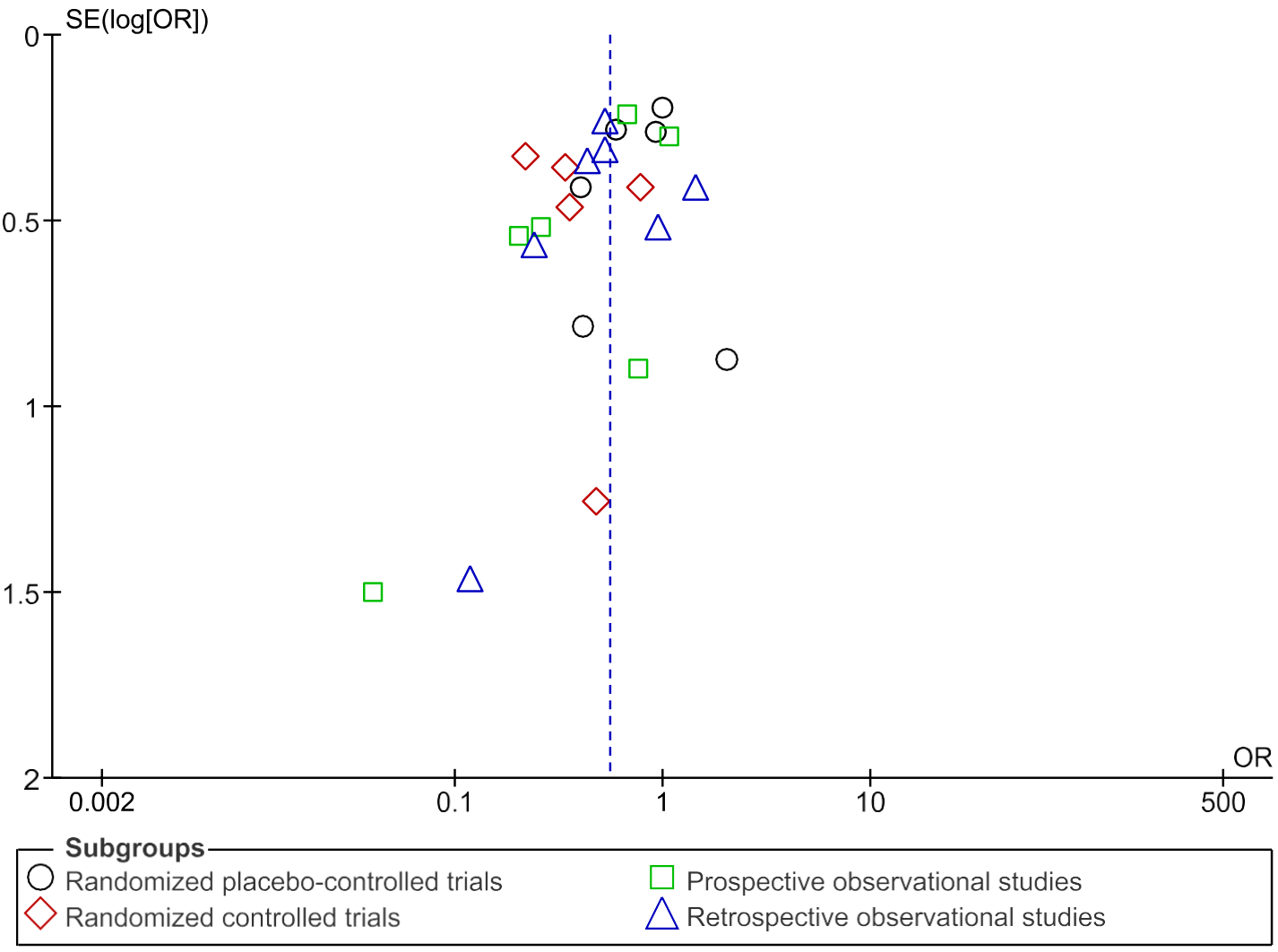


**Figure S2. Impact of mineralocorticoid receptor antagonists (MRAs) versus control in newly atrial fibrillation onset versus atrial fibrillation recurrence.**

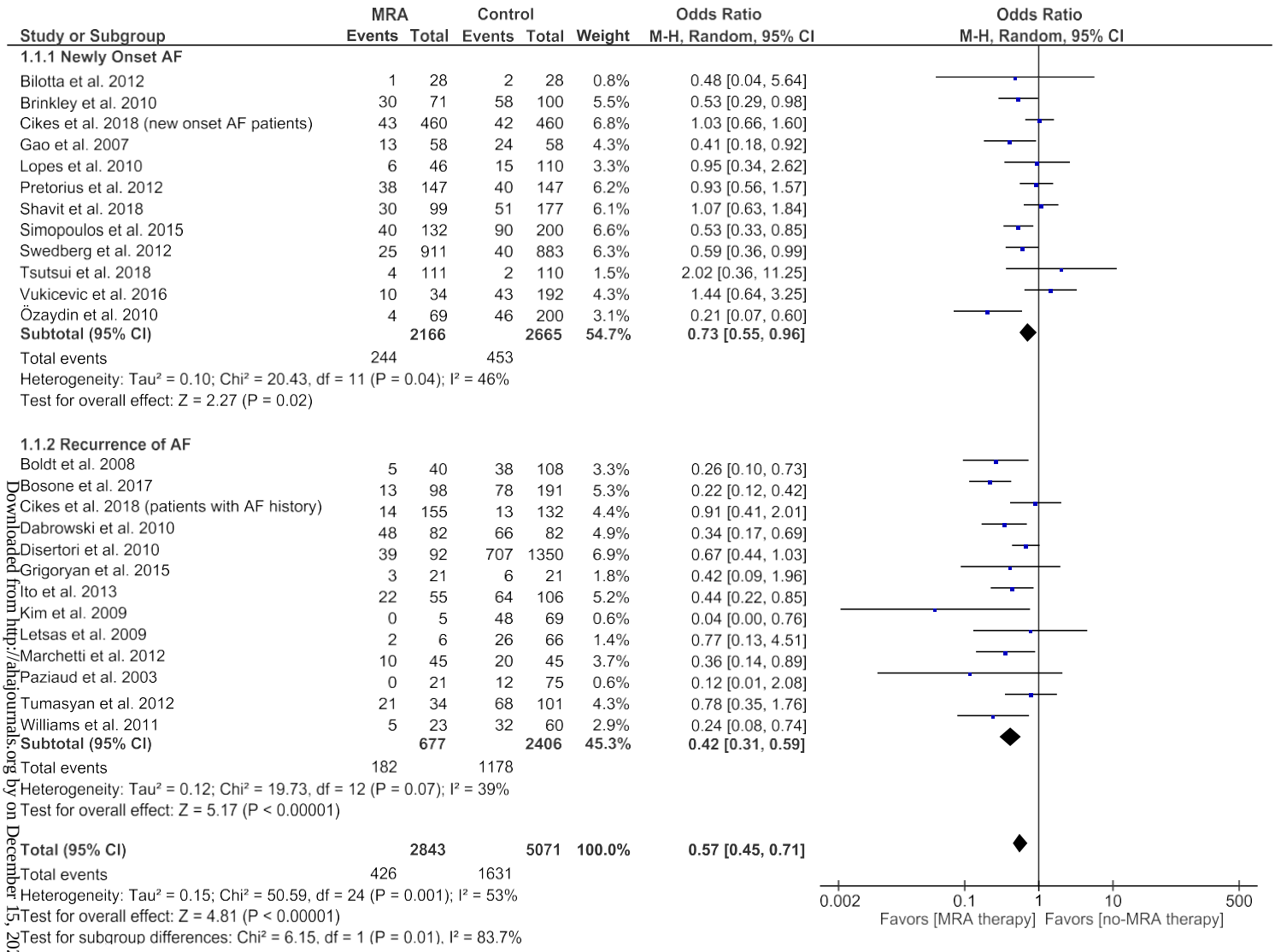


**Figure S3. Impact of mineralocorticoid receptor antagonists (MRAs) on AF occurrence versus that of controls in the presence of HFrEF or not (defined as patients with LVEF ≤40% and class NYHA ≥2).**

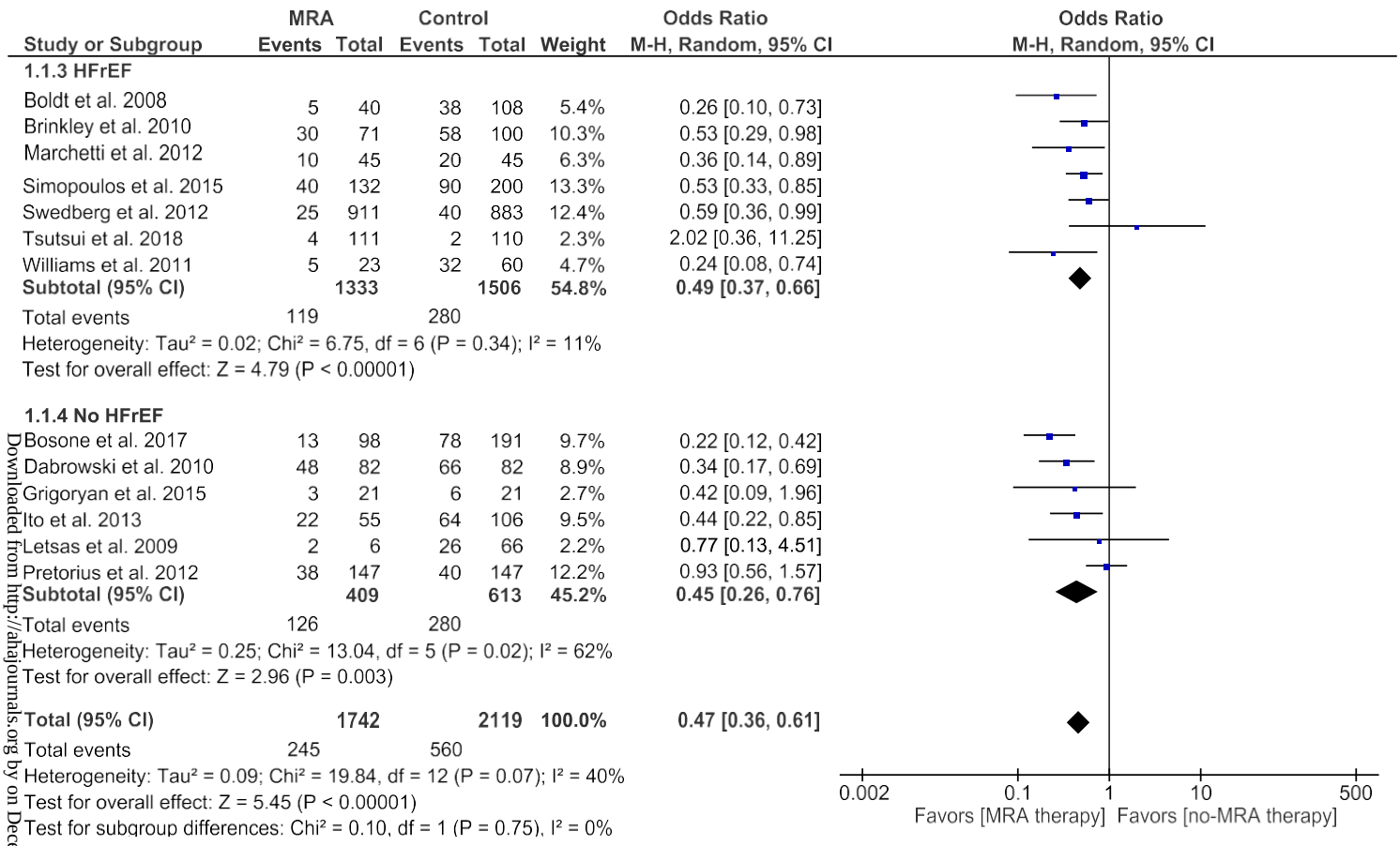


**Figure S4. Impact of mineralocorticoid receptor antagonists (MRAs) on AF occurrence versus that of controls in full-text published versus meetings abstracts or unpublished studies.**

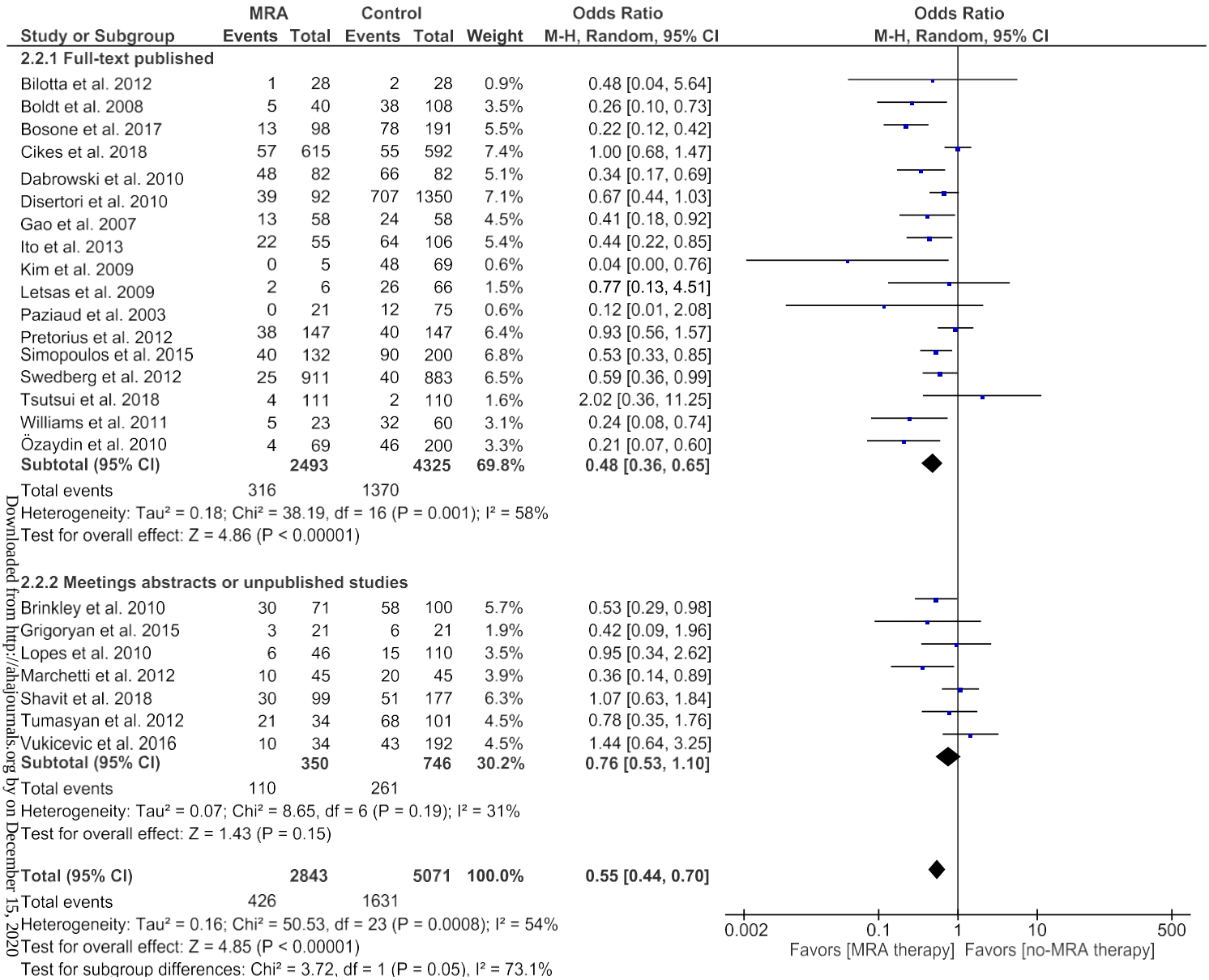


**Figure S5. Impact of mineralocorticoid receptor antagonists (MRAs) on AF occurrence versus that of controls regarding the risk of bias of studies (evaluated by omitting studies judged to be at least at a high or serious risk of bias).**

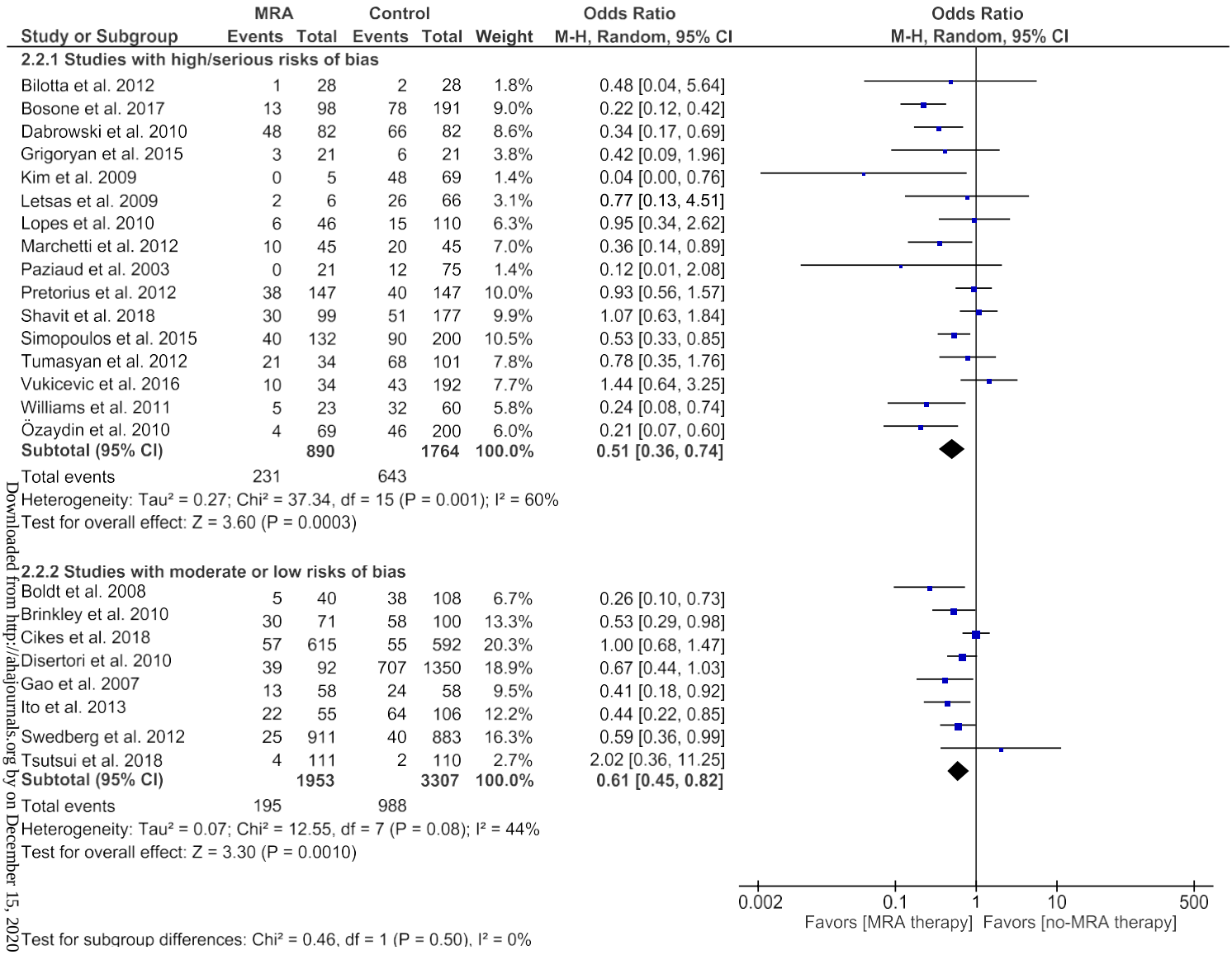


**Figure S6. Impact of mineralocorticoid receptor antagonists (MRAs) on AF occurrence versus that of controls regarding the funding sources.**

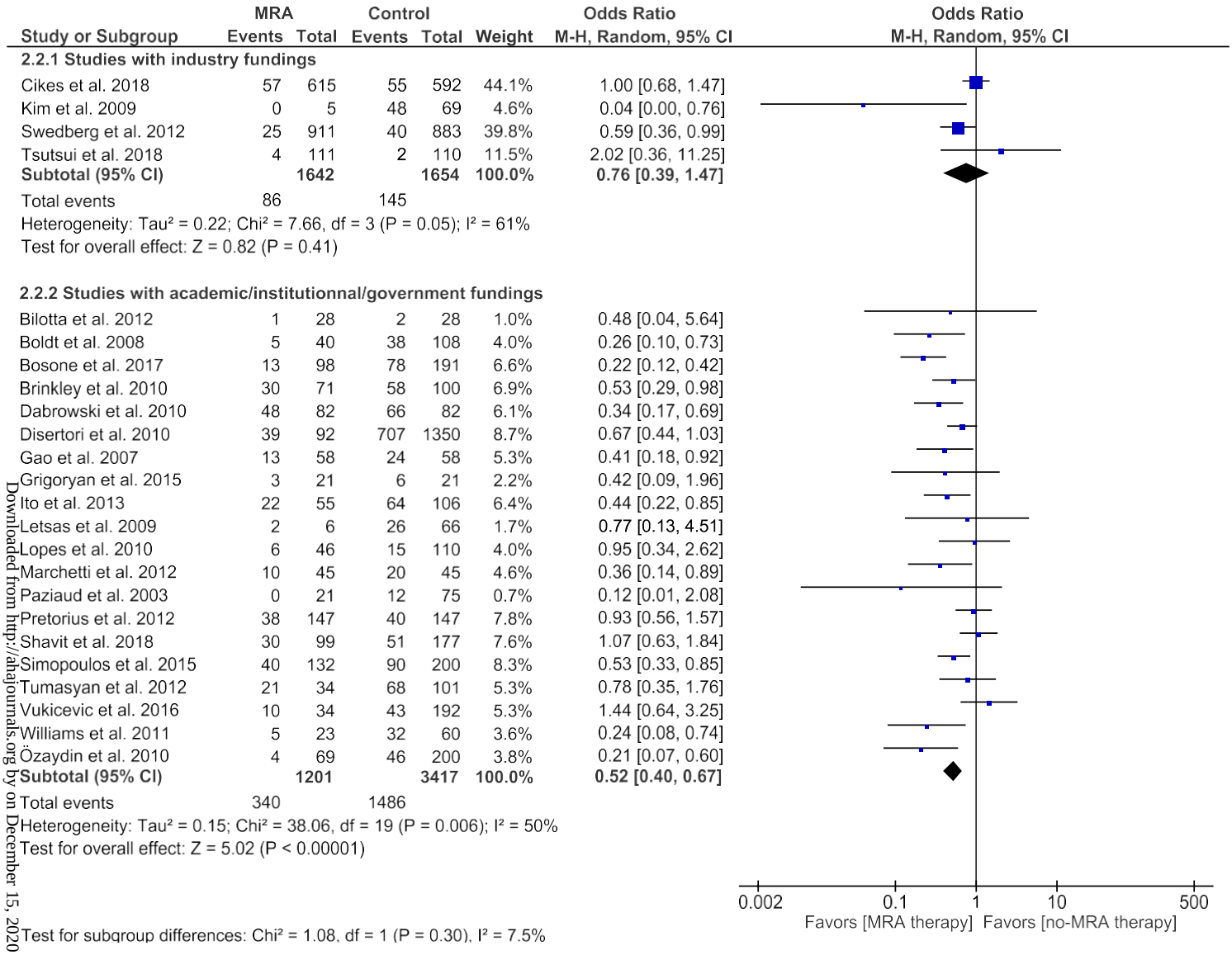


**Figure S7. Impact of mineralocorticoid receptor antagonists (MRAs) on AF occurrence versus that of controls among the MRAs used (spironolactone, eplerenone, canrenone or unspecified MRA).**

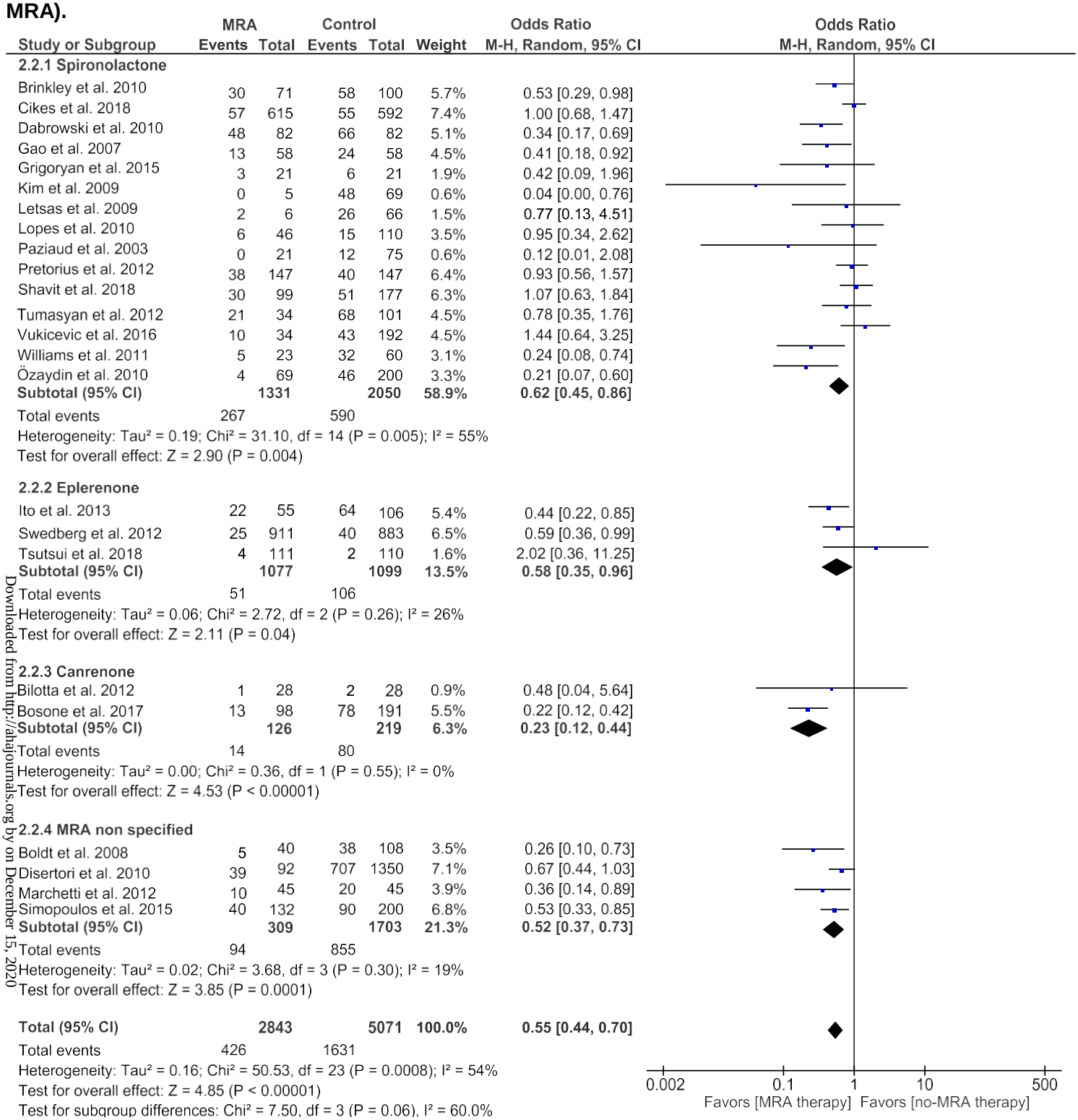


**Figure S8. Impact of mineralocorticoid receptor antagonists (MRAs) on AF occurrence versus that of controls in the following subgroups: newly postoperative atrial fibrillation (POAF) onset, AF recurrence after electrical cardioversion, and AF recurrence after catheter ablation.**

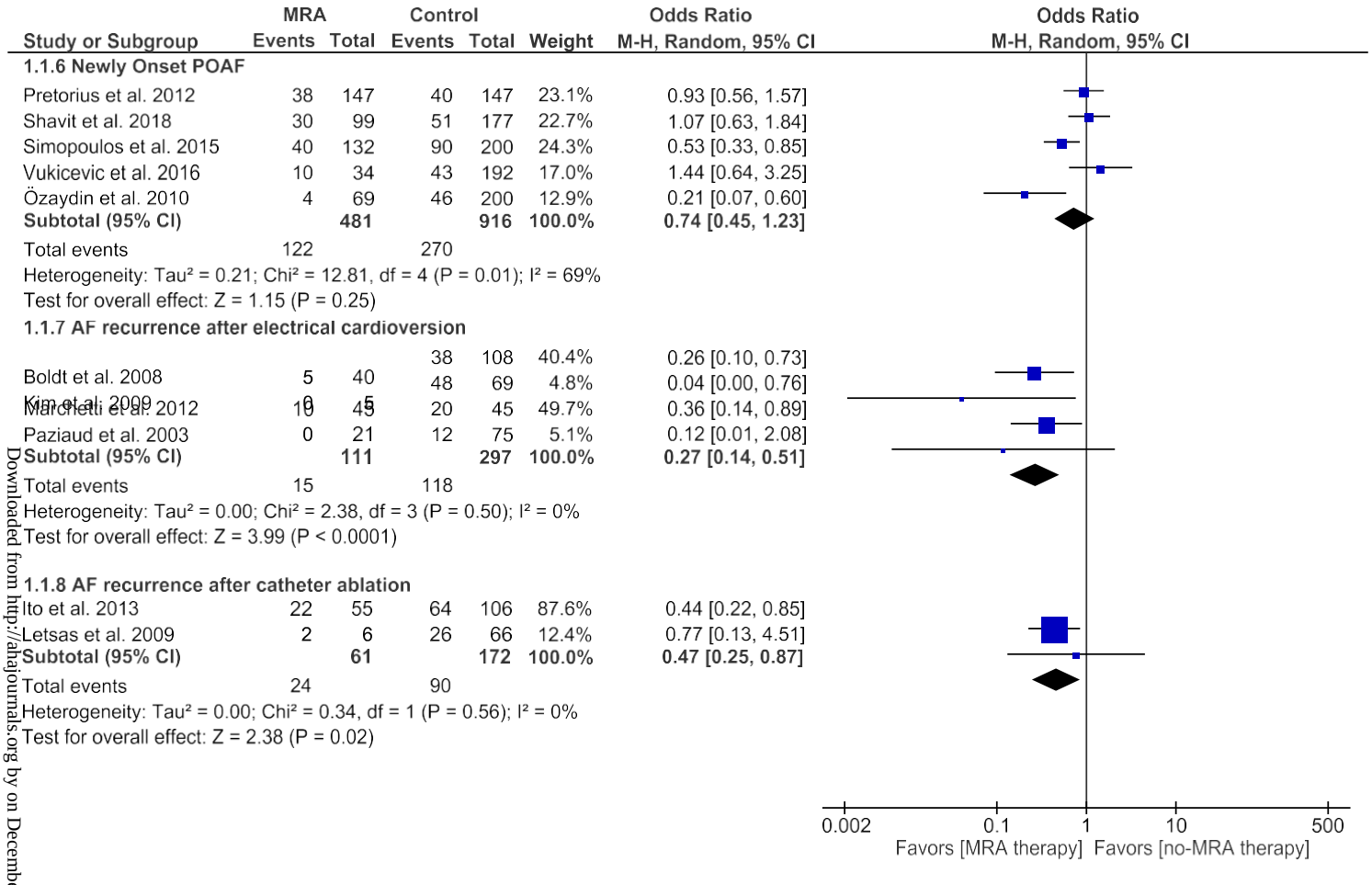


**Figure S9. Impact of mineralocorticoid receptor antagonists (MRAs) on AF occurrence versus that of controls in POAF and no-POAF studies.**

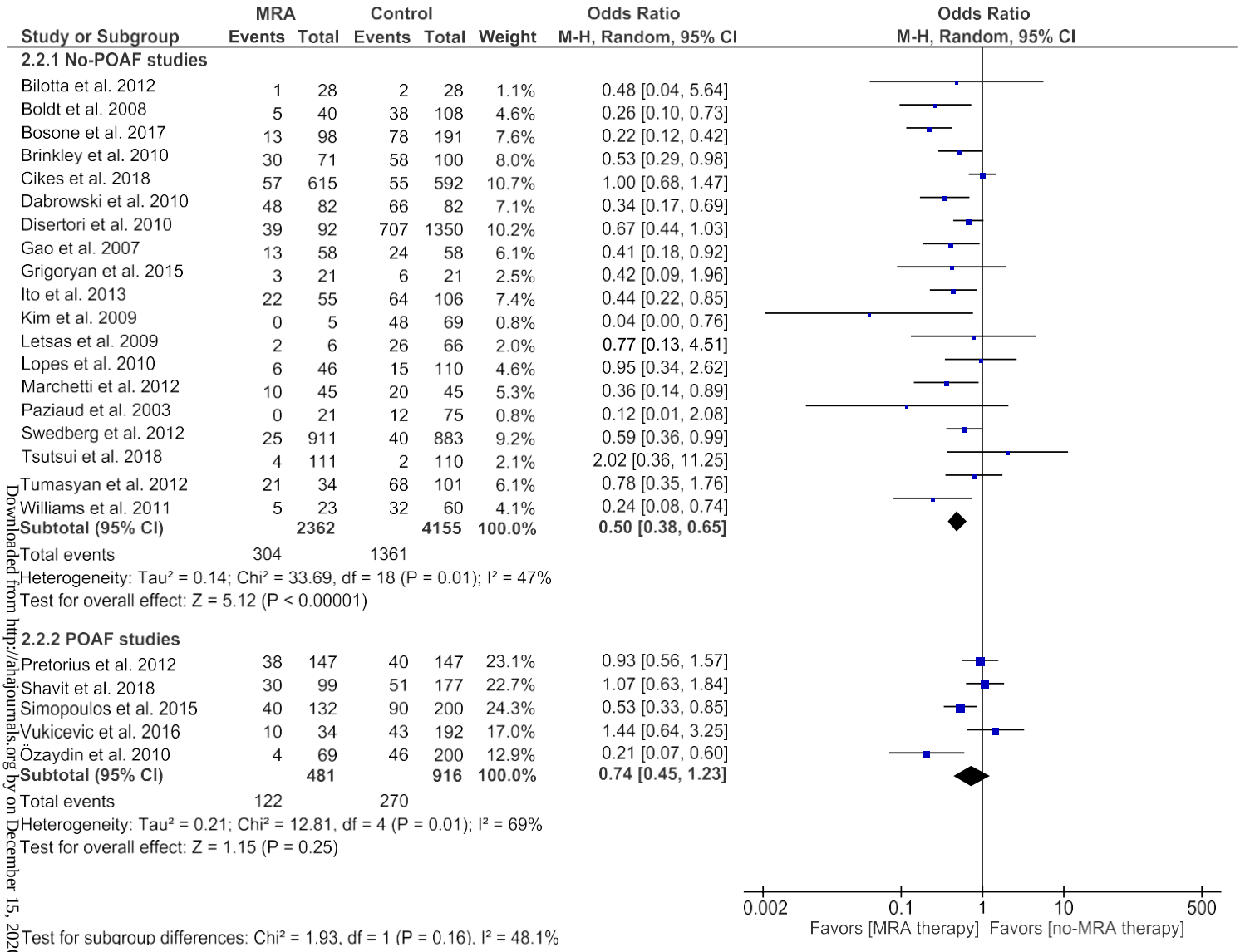
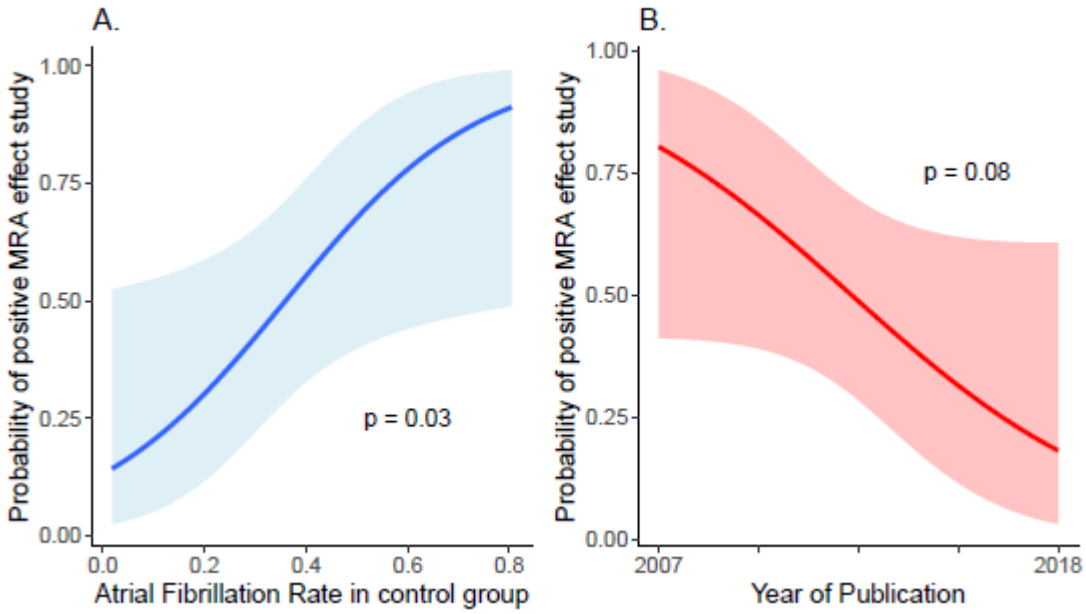
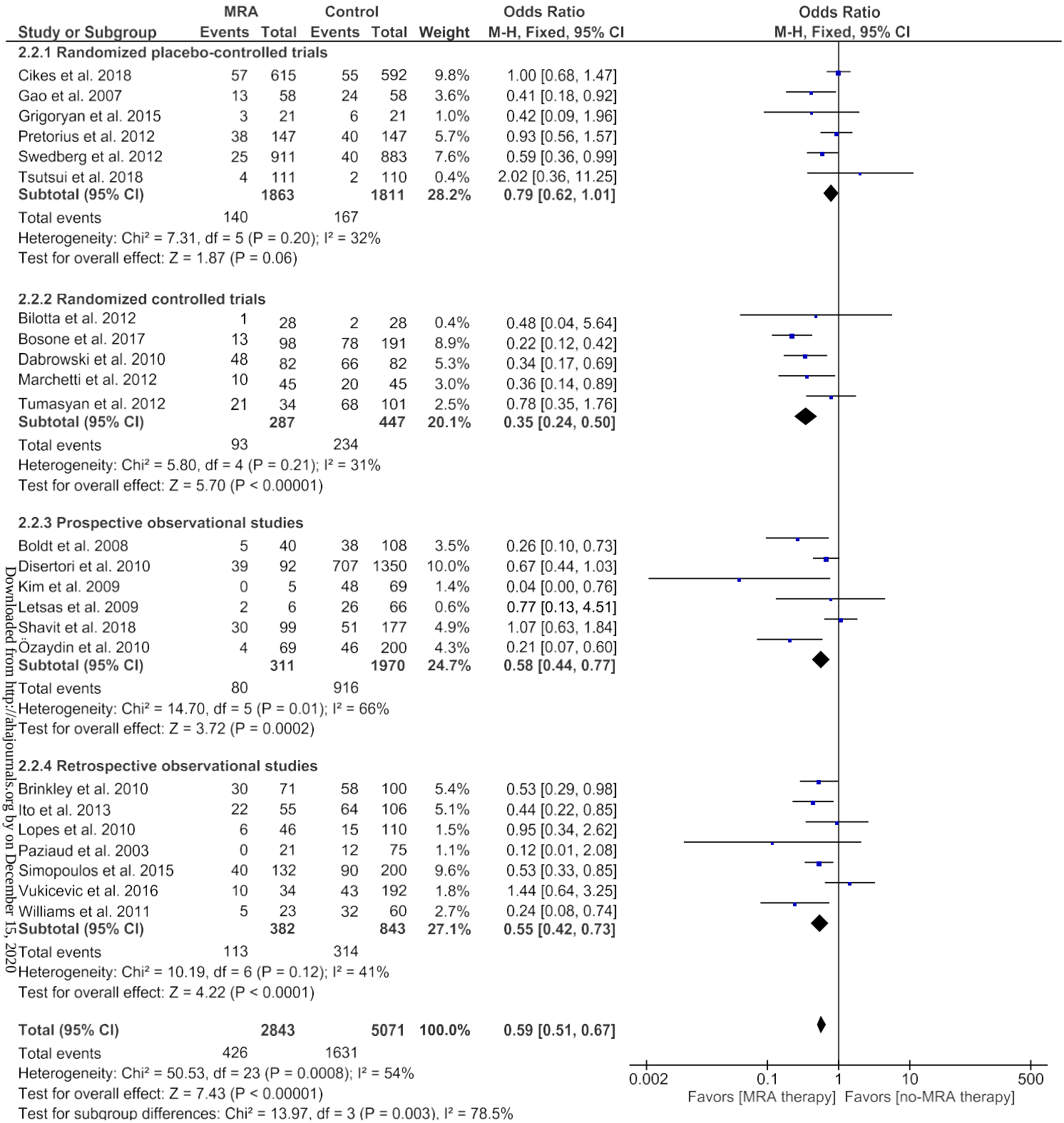


**Figure S10. AF occurrence rate in the control group was significantly calibrated to predict the positive effect of MRA therapy on AF occurrence (panel A).**




The year of publication of the study was not significantly calibrated to predict a positive MRA effect on AF occurrence (panel B).

**Figure S11. Atrial fibrillation occurrence comparing mineralocorticoid receptor antagonists (MRAs) therapy versus controls using a fixed effect model.**



**Supplemental References:**


1. Paziaud O, Piot O, Rousseau J, Copie X, Lavergne T, Guize L, Le Heuzey JY. External electrical cardioversion of atrial arrhythmia: predictive criteria of success. *Ann Cardiol Angeiol (Paris)* 2003;52:232–8.

2. Gao X, Peng L, Adhikari CM, Lin J, Zuo Z. Spironolactone reduced arrhythmia and maintained magnesium homeostasis in patients with congestive heart failure. *J Card Fail* 2007;13:170–7.

3. Boldt L-H, Rolf S, Huemer M, Parwani AS, Luft FC, Dietz R, Haverkamp W. Optimal heart failure therapy and successful cardioversion in heart failure patients with atrial fibrillation. *Am Heart J* 2008;155:890–5.

4. Kim SK, Pak H-N, Park JH, Ko KJ, Lee JS, Choi JI, Kim YH. Clinical and serological predictors for the recurrence of atrial fibrillation after electrical cardioversion. *Europace* 2009;11:1632–8.

5. Letsas KP, Weber R, Bürkle G, Mihas CC, Minners J, Kalusche D, Arentz T. Pre-ablative predictors of atrial fibrillation recurrence following pulmonary vein isolation: the potential role of inflammation. *Europace* 2009;11:158–63.

6. Brinkley D, Chen J. Poster PO4-12: Effect of spironolactone on atrial fibrillation in patients with heart failure. *Heart Rhythm* 2010;7:S262.

7. Dabrowski R, Borowiec A, Smolis-Bak E, Kowalik I, Sosnowski C, Kraska A, Kazimierska B, Wozniak J, Zareba W, Szwed H. Effect of combined spironolactone-β-blocker ± enalapril treatment on occurrence of symptomatic atrial fibrillation episodes in patients with a history of paroxysmal atrial fibrillation (SPIR-AF study). *Am J Cardiol* 2010;106:1609–14.

8. Disertori M, Lombardi F, Barlera S, Latini R, Maggioni AP, Zeni P, Di Pasquale G, Cosmi F, Franzosi MG; GISSI-AF Investigators. Clinical predictors of atrial fibrillation recurrence in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Atrial Fibrillation (GISSI-AF) trial. *Am Heart J* 2010;159:857–63.

9. Lopes R, Lourenco P, Paulo C, Sousa A, Lebreiro A, Mascarenhas J, Silva S, Santos M, Silva H, Bettencourt P. Is there a role for spironolactone in atrial fibrillation prevention? *European Journal of Heart Failure Supplements* 2010;9:S145.

10. Ozaydin M, Varol E, Türker Y, Peker O, Erdoğan D, Doğan A, Ibrişim E. Association between renin-angiotensin-aldosterone system blockers and postoperative atrial fibrillation in patients with mild and moderate left ventricular dysfunction. *Anadolu Kardiyol Derg* 2010;10:137–42.

11. Williams RS, deLemos JA, Dimas V, Reisch J, Hill JA, Naseem RH. Effect of spironolactone on patients with atrial fibrillation and structural heart disease.
*Clin Cardiol* 2011;34:415–9.

12. Bilotta F, Giovannini F, Aghilone F, Stazi E, Titi L, Zeppa IO, Rosa G. Potassium sparing diuretics as adjunct to mannitol therapy in neurocritical care patients with cerebral edema: effects on potassium homeostasis and cardiac arrhythmias. *Neurocrit Care* 2012;16:280–5.

13. Marchetti G, Roncuzzi R, Gambetti S, Poci M., Zaniboni A, Urbinati S. Electrical cardioversion at first episode of Atrial Fibrillation in patients with heart failure. ESC Congr. 2012 - P2365.

14. Pretorius M, Murray KT, Yu C, Byrne JG, Billings FT, Petracek MR, Greelish JP, Hoff SJ, Ball SK,

Mishra V, Body SC, Brown NJ. Angiotensin-converting enzyme inhibition or mineralocorticoid receptor blockade do not affect prevalence of atrial fibrillation in patients undergoing cardiac surgery. *Crit Care Med* 2012;40:2805–12.

15. Swedberg K, Zannad F, McMurray JJV, Krum H, Veldhuisen DJ van, Shi H, Vincent J, Pitt B; EMPHASIS-HF Study Investigators. Eplerenone and atrial fibrillation in mild systolic heart failure: results from the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure) study. *J Am Coll Cardiol* 2012;59:1598–603.

16. Tumasyan L, Adamyan K, Chilingaryan A. Poster 853: Comparative efficacy of renin-angiotensin system modulators on sinus rhythm restoration in chronic heart failure patients with atrial fibrillation. *Eur Heart J - Cardiovasc Imaging* 2012;13:i143–65.

17. Ito Y, Yamasaki H, Naruse Y, Yoshida K, Kaneshiro T, Murakoshi N, Igarashi M, Kuroki K, Machino T, Xu D, Kunugita F, Sekiguchi Y, Sato A, Tada H, Aonuma K. Effect of eplerenone on maintenance of sinus rhythm after catheter ablation in patients with long-standing persistent atrial fibrillation. *Am J Cardiol* 2013;111:1012–8.

18. Grigoryan S, Hazarapetyan L. Acute Cardiovascular Care 2015 - P 224 The impact of spirolactone therapy on recurrence and atrial structural remodeling in patients with paroxysmal atrial fibrillation. *Eur Heart J Acute Cardiovasc Care* 2015;4:89.

19. Simopoulos V, Tagarakis G, Hatziefthimiou A, Skoularigis I, Triposkiadis F, Trantou V, Tsilimingas N, Aidonidis I. Effectiveness of aldosterone antagonists for preventing atrial fibrillation after cardiac surgery in patients with systolic heart failure: a retrospective study. *Clin Res Cardiol* 2015;104:31–7.

20. Vukicevic MV, Putnik S, Potpara TS. GW27-e0978 The relationship between preoperative pharmacotherapy and incident postoperative atrial fibrillation in patients undergoing isolated coronary artery bypass grafting. *J Am Coll Cardiol* 2018;68:C120.

21. Bosone D, Costa A, Ghiotto N, Ramusino MC, Zoppi A, D'Angelo A, Fogari R. Effect of ramipril/hydrochlorothiazide and ramipril/canrenone combination on atrial fibrillation recurrence in hypertensive type 2 diabetic patients with and without cardiac autonomic neuropathy. *Arch Med Sci* 2017;13:550–7.

22. Cikes M, Claggett B, Shah AM, Desai AS, Lewis EF, Shah SJ, Anand IS, O'Meara E, Rouleau JL, Sweitzer NK, Fang JC, Saksena S, Pitt B, Pfeffer MA, Solomon SD. Atrial Fibrillation in Heart Failure With Preserved Ejection Fraction: The TOPCAT Trial. *JACC Heart Fail* 2018;6:689–97.

23. Tsutsui H, Ito H, Kitakaze M, Komuro I, Murohara T, Izumi T, Sunagawa K, Yasumura Y, Yano M, Yamamoto K, Yoshikawa T, Tsutamoto T, Zhang J, Okayama A, Ichikawa Y, Kanmuri K, Matsuzaki M, J-EMPHASIS-HF Study Group. Double-Blind, Randomized, Placebo-Controlled Trial Evaluating the Efficacy and Safety of Eplerenone in Japanese Patients With Chronic Heart Failure (J-EMPHASIS-HF). *Circ J* 2017;82:148–58.

24. Shavit L, Silberman S, Tauber R, Merin O, Bitran D, Fink D. Preoperative aldosterone receptor blockade and outcomes of cardiac surgery in patients with chronic kidney disease. *Clin Nephrol* 2018;89:187–95.