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

| Section/topic                      | #  | Checklist item                                                                                                                                                                                                 | Reported section # (top-level heading)                           |
|-----------------------------------|----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------|
| **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                                           |
| **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,          |
| 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](http://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          | 0.56, 95% CI 0.44-0.71                                                                   | 0.6                             |
| Gao et al. 2007              | 0.56, 95% CI 0.44-0.72                                                                   | 4.5                             |
| Boldt et al. 2008            | 0.57, 95% CI 0.45-0.72                                                                   | 3.5                             |
| Kim et al. 2009              | 0.56, 95% CI 0.45-0.71                                                                   | 0.6                             |
| Letsas et al. 2009           | 0.55, 95% CI 0.43-0.70                                                                   | 1.5                             |
| Brinkley et al. 2010         | 0.55, 95% CI 0.43-0.71                                                                   | 5.7                             |
| Dabrowski et al. 2010 (SPIR-AF) | 0.57, 95% CI 0.45-0.73                                                                 | 5.1                             |
| Disertori et al. 2010 (GFFI-AF) | 0.54, 95% CI 0.42-0.70                                                                   | 7.1                             |
| Lopes et al. 2010            | 0.54, 95% CI 0.42-0.69                                                                   | 3.5                             |
| Özaydin et al. 2010          | 0.57, 95% CI 0.45-0.73                                                                   | 3.3                             |
| Williams et al. 2011         | 0.57, 95% CI 0.45-0.72                                                                   | 3.1                             |
| Billota et al. 2012          | 0.55, 95% CI 0.43-0.71                                                                   | 0.9                             |
| Marchetti et al. 2012         | 0.56, 95% CI 0.44-0.72                                                                   | 3.9                             |
| Pretorius et al. 2012        | 0.53, 95% CI 0.42-0.68                                                                   | 6.4                             |
| Swedberg et al. 2012 (EMPHASIS-AF) | 0.55, 95% CI 0.42-0.71                                                                 | 6.5                             |
| Tumasyan et al. 2012         | 0.54, 95% CI 0.42-0.70                                                                   | 4.5                             |
| Ito et al. 2013              | 0.56, 95% CI 0.44-0.72                                                                   | 5.4                             |
| Grigoryan et al. 2015        | 0.56, 95% CI 0.44-0.71                                                                   | 1.9                             |
| Simopoulos et al. 2015       | 0.55, 95% CI 0.43-0.71                                                                   | 6.8                             |
| Vukicevic et al. 2016        | 0.53, 95% CI 0.42-0.67                                                                   | 4.5                             |
| Bosone et al. 2017           | 0.59, 95% CI 0.47-0.74                                                                   | 5.5                             |
| Cikes et al. 2018 (TOPCAT)   | 0.53, 95% CI 0.42-0.67                                                                   | 7.4                             |
| Tsutsui et al. 2018 (J-EMPHASIS-HF) | 0.54, 95% CI 0.43-0.69                                                                 | 1.6                             |
| Shavit et al. 2018           | 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    | Unclear risk               | Unclear risk           | High risk                   | High risk  | High risk                              | High risk                   | Unclear risk           |
| Bosone et al. 2017     | Unclear risk               | High risk              | Low risk                    | Low risk   | Low risk                               | Low risk                    | Low risk               |
| Dabrowski et al. 2010  | Unclear risk               | Unclear risk           | Low risk                    | Low risk   | High risk                              | Unclear risk               | Low risk               |
| Gao et al. 2007        | Unclear risk               | Unclear risk           | Low risk                    | Low risk   | Low risk                               | Unclear risk               | Low risk               |
| Grigoryan et al. 2015  | Unclear risk               | Unclear risk           | High risk                   | Unclear risk | Low risk                               | Unclear risk               | Low risk               |
| Marchetti et al. 2012  | Unclear risk               | Unclear risk           | High risk                   | High risk  | Unclear risk                           | High risk                   | Unclear risk           |
| Cikes et al. 2018      | Low risk                   | Low risk               | Low risk                    | Low risk   | Low risk                               | Low risk                    | Low risk               |
| Pretorius et al. 2012  | Low risk                   | Low risk               | Low risk                    | High risk  | Low risk                               | Low risk                    | Low risk               |
| Swedberg et al. 2012   | Low risk                   | Low risk               | Low risk                    | Low risk   | Low risk                               | Low risk                    | Low risk               |
| Tsutsui et al. 2018    | Low risk                   | Low risk               | Low risk                    | Low risk   | Low risk                               | Low risk                    | Low risk               |
| Tumasyan et al. 2012   | 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. 2008³     | Low risk                | Moderate risk                    | Moderate risk                            | Moderate risk                                     | Low risk                | Low risk                         | Low risk                               | Low risk     |
| Brinkley et al. 2010⁶  | Moderate risk           | Moderate risk                    | Low risk                                 | Low risk                                          | Not interpretable       | Low risk                         | Low risk                               | Low risk     |
| Disertori et al. 2010⁸ | Low risk                | Moderate risk                    | Low risk                                 | Low risk                                          | Low risk                | Low risk                         | Low risk                               | Low risk     |
| Ito et al. 2013¹⁷      | Low risk                | Moderate risk                    | Low risk                                 | Moderate risk                                     | Low risk                | Low risk                         | Low risk                               | Low risk     |
| Kim et al. 2009⁴       | Low risk                | Moderate risk                    | Moderate risk                            | Serious risk                                      | Low risk                | Low risk                         | Low risk                               | Low risk     |
| Letsas et al. 2009⁵    | Moderate risk           | Low risk                         | Serious risk                             | Serious risk                                      | Low risk                | Low risk                         | Low risk                               | Low risk     |
| Lopes et al. 2010⁹     | Moderate risk           | Moderate risk                    | Moderate risk                            | Serious risk                                      | Low risk                | Low risk                         | Low risk                               | Low risk     |
| Özaydin et al. 2010¹⁰  | Low risk                | Moderate risk                    | Moderate risk                            | Serious risk                                      | Not interpretable       | Serious risk                     | Low risk                               | Moderate risk |
| Paziaud et al. 2003¹    | Moderate risk           | Moderate risk                    | Serious risk                             | Serious risk                                      | Low risk                | Low risk                         | Low risk                               | Low risk     |
| Shavit et al. 2018²⁴   | Low risk                | Moderate risk                    | Serious risk                             | Serious risk                                      | Moderate risk           | Low risk                         | Low risk                               | Low risk     |
| Simopoulos et al. 2015¹⁹| Moderate risk           | Moderate risk                    | Serious risk                             | Moderate risk                                     | Low risk                | Low risk                         | Low risk                               | Low risk     |
| Vukicevic et al. 2016²⁰| Moderate risk           | Moderate risk                    | Serious risk                             | Not interpretable                                 | Low risk                | Low risk                         | Low risk                               | Low risk     |
| Williams et al. 2011¹¹ | Moderate risk           | Moderate risk                    | Serious risk                             | Moderate risk                                     | Low 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.

| Study or Subgroup | MRA Events Total | Control Events Total | Weight | Odds Ratio M-H, Random, 95% CI | Odds Ratio M-H, Random, 95% CI |
|-------------------|------------------|----------------------|--------|--------------------------------|--------------------------------|
| **1.1 Newly Onset AF** |                  |                      |        |                                |                                |
| Bilotta et al. 2012 | 1 28             | 2 28                 | 0.8%   | 0.48 [0.04, 5.64]              |                                |
| Brinkley et al. 2010 | 30 71            | 58 100               | 5.5%   | 0.53 [0.11, 2.46]              |                                |
| Cikes et al. 2018 (new onset AF patients) | 43 480          | 42 460               | 6.8%   | 1.03 [0.66, 1.60]              |                                |
| Gao et al. 2007 | 13 56             | 24 58                | 4.3%   | 0.41 [0.18, 0.92]              |                                |
| Lopes et al. 2010 | 6 46             | 15 110               | 3.3%   | 0.95 [0.34, 2.62]              |                                |
| Pretorius et al. 2012 | 38 147          | 40 147               | 6.2%   | 0.93 [0.56, 1.57]              |                                |
| Shavit et al. 2018 | 30 99            | 51 177               | 6.1%   | 1.07 [0.63, 1.84]              |                                |
| Simopoulos et al. 2015 | 40 132         | 90 200               | 6.6%   | 0.83 [0.33, 0.89]              |                                |
| Swedberg et al. 2012 | 25 911          | 40 883               | 6.3%   | 0.59 [0.36, 0.99]              |                                |
| Tsutsui et al. 2018 | 4 111            | 2 110                | 1.5%   | 2.02 [0.36, 12.26]             |                                |
| Vukicevic et al. 2016 | 10 34           | 43 192               | 4.3%   | 1.44 [0.64, 2.35]              |                                |
| Özaydin et al. 2010 | 4 69             | 46 200               | 3.1%   | 0.21 [0.07, 0.60]              |                                |
| **Subtotal (95% CI)** | 2166 2665        | 54.7%                |        | 0.73 [0.55, 0.96]              |                                |

Total events 244 453
Heterogeneity: Tau² = 0.10; Chi² = 20.43, df = 11 (P = 0.04); I² = 46%
Test for overall effect: Z = 2.27 (P = 0.02)

**1.2 Recurrence of AF**

| Study or Subgroup | MRA Events Total | Control Events Total | Weight | Odds Ratio M-H, Random, 95% CI | Odds Ratio M-H, Random, 95% CI |
|-------------------|------------------|----------------------|--------|--------------------------------|--------------------------------|
| Boldt et al. 2008 | 5 40             | 38 108               | 3.3%   | 0.26 [0.10, 0.73]              |                                |
| Bosone et al. 2017 | 13 98            | 78 191               | 5.3%   | 0.22 [0.12, 0.42]              |                                |
| Cikes et al. 2018 (patients with AF history) | 14 155          | 13 132               | 4.4%   | 0.91 [0.41, 2.01]              |                                |
| Dabrowski et al. 2010 | 48 82           | 66 82                | 4.9%   | 0.34 [0.17, 0.69]              |                                |
| Disertori et al. 2010 | 39 92           | 707 1350             | 6.9%   | 0.67 [0.44, 1.03]              |                                |
| Grigoryan et al. 2015 | 3 21            | 6 21                 | 1.8%   | 0.42 [0.09, 1.96]              |                                |
| Ito et al. 2013 | 22 55            | 64 106               | 5.2%   | 0.44 [0.22, 0.85]              |                                |
| Kim et al. 2009 | 0 5              | 48 69                | 0.6%   | 0.04 [0.00, 0.76]              |                                |
| Letsas et al. 2009 | 2 6              | 26 66                | 1.4%   | 0.77 [0.13, 4.51]              |                                |
| Marchetti et al. 2012 | 10 45           | 20 45                | 3.7%   | 0.36 [0.14, 0.89]              |                                |
| Paziaud et al. 2003 | 0 21             | 12 75                | 0.6%   | 0.12 [0.01, 2.08]              |                                |
| Turnasyan et al. 2012 | 21 34           | 68 101               | 4.3%   | 0.78 [0.35, 1.76]              |                                |
| Williams et al. 2011 | 5 23            | 32 60                | 2.9%   | 0.24 [0.08, 0.74]              |                                |
| **Subtotal (95% CI)** | 677 2466        | 45.3%                |        | 0.42 [0.31, 0.59]              |                                |

Total events 182 1178
Heterogeneity: Tau² = 0.12; Chi² = 19.73, df = 12 (P = 0.07); I² = 39%
Test for overall effect: Z = 5.17 (P < 0.00001)

Total (95% CI) 2843 5071 100.0% 0.57 [0.45, 0.71]

Total events 426 1631
Heterogeneity: Tau² = 0.15; Chi² = 50.59, df = 24 (P = 0.001); I² = 53%
Test for overall effect: Z = 4.81 (P < 0.00001)
Test for subgroup differences: Chi² = 6.15, df = 1 (P = 0.01), I² = 83.7%
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).

| Study or Subgroup     | MRA Events | Control Events | Weight | Odds Ratio M-H, Random, 95% CI | Odds Ratio M-H, Random, 95% CI |
|------------------------|------------|----------------|--------|-------------------------------|-------------------------------|
| **1.1.3 HFrEF**        |            |                |        |                               |                               |
| Boldt et al. 2008      | 5          | 40             | 108    | 5.4% 0.26 [0.10, 0.73]         |                               |
| Brinkley et al. 2010   | 30         | 71             | 50     | 10.3% 0.53 [0.29, 0.98]        |                               |
| Marchetti et al. 2012  | 10         | 45             | 20     | 13.5% 0.59 [0.29, 0.98]        |                               |
| Simopoulos et al. 2015 | 60         | 132            | 20     | 13.3% 0.53 [0.33, 0.85]        |                               |
| Swedberg et al. 2012   | 25         | 911            | 40     | 12.4% 0.59 [0.36, 0.99]        |                               |
| Tsutsui et al. 2018    | 4          | 111            | 2      | 2.3% 2.02 [0.38, 11.25]        |                               |
| Williams et al. 2011   | 5          | 23             | 32     | 4.7% 0.24 [0.08, 0.74]         |                               |
| **Subtotal (95% CI)**  | 1333       | 1506           | 54.8% 0.49 [0.37, 0.66]        |                               |

Total events 119 280
Heterogeneity: Tau² = 0.02; Chi² = 6.75, df = 6 (P = 0.34); I² = 11%
Test for overall effect: Z = 4.79 (P < 0.00001)

| **1.1.4 No HFrEF**     |            |                |        |                               |                               |
| Bosone et al. 2017     | 13         | 98             | 78     | 9.7% 0.22 [0.12, 0.42]         |                               |
| Dabrowski et al. 2010  | 48         | 82             | 66     | 8.9% 0.34 [0.17, 0.69]         |                               |
| Grigoryan et al. 2015  | 3          | 21             | 6      | 2.7% 0.42 [0.09, 1.96]         |                               |
| Ito et al. 2013        | 22         | 55             | 64     | 9.5% 0.44 [0.22, 0.85]         |                               |
| Letsas et al. 2009     | 2          | 6              | 26     | 2.2% 0.77 [0.13, 4.51]         |                               |
| Pretorius et al. 2012  | 38         | 147            | 40     | 12.2% 0.93 [0.56, 1.57]        |                               |
| **Subtotal (95% CI)**  | 409        | 613            | 45.2% 0.45 [0.26, 0.76]        |                               |

Total events 126 280
Heterogeneity: Tau² = 0.25; Chi² = 13.04, df = 5 (P = 0.02); I² = 62%
Test for overall effect: Z = 2.96 (P = 0.003)

Total (95% CI) 1742 2119 100.0% 0.47 [0.36, 0.61]
Total events 245 560
Heterogeneity: Tau² = 0.09; Chi² = 19.84, df = 12 (P = 0.07); I² = 40%
Test for overall effect: Z = 5.45 (P < 0.00001)
Test for subgroup differences: Chi² = 0.10, df = 1 (P = 0.75), I² = 0%
### 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.

| Study or Subgroup | MRA Events | Control Events | Total Events | Weight | Odds Ratio M-H, Random, 95% CI | Odds Ratio M-H, Random, 95% CI |
|-------------------|------------|----------------|--------------|--------|--------------------------------|--------------------------------|
| **2.2.1 Full-text published** |            |                |              |        |                                |                                |
| Bilotta et al. 2012 | 1          | 28             | 28           | 0.9%   | 0.48 [0.04, 5.64]              |                                |
| Boldt et al. 2008  | 5          | 40             | 45           | 3.5%   | 0.26 [0.10, 0.73]              |                                |
| Bosone et al. 2017 | 13         | 98             | 111          | 5.5%   | 0.22 [0.12, 0.42]              |                                |
| Cikes et al. 2018  | 57         | 615            | 672          | 7.4%   | 1.00 [0.68, 1.47]              |                                |
| Dabrowski et al. 2010 | 48       | 82             | 130          | 5.1%   | 0.34 [0.17, 0.69]              |                                |
| Di Sertori et al. 2010 | 39       | 92             | 131          | 7.1%   | 0.67 [0.44, 1.03]              |                                |
| Gao et al. 2007    | 13         | 58             | 71           | 4.5%   | 0.41 [0.18, 0.92]              |                                |
| Ito et al. 2013    | 22         | 55             | 77           | 5.4%   | 0.44 [0.22, 0.85]              |                                |
| Kim et al. 2009    | 5          | 48             | 53           | 0.6%   | 0.04 [0.00, 0.76]              |                                |
| Letsas et al. 2009 | 2          | 26             | 28           | 1.5%   | 0.77 [0.13, 4.51]              |                                |
| Paziaud et al. 2003 | 0          | 21             | 21           | 0.6%   | 0.12 [0.01, 2.08]              |                                |
| Pretrouis et al. 2012 | 38      | 147            | 185          | 6.4%   | 0.93 [0.56, 1.57]              |                                |
| Simopoulos et al. 2015 | 40       | 132            | 172          | 6.8%   | 0.53 [0.33, 0.85]              |                                |
| Swedberg et al. 2012 | 25       | 911            | 936          | 6.5%   | 0.59 [0.36, 0.99]              |                                |
| Tsutsui et al. 2018 | 4          | 111            | 115          | 1.6%   | 2.02 [0.36, 11.25]             |                                |
| Williams et al. 2011 | 5         | 23             | 28           | 3.1%   | 0.24 [0.08, 0.74]              |                                |
| Özyaydin et al. 2010 | 4         | 69             | 73           | 3.3%   | 0.21 [0.07, 0.60]              |                                |
| **Subtotal (95% CI)** | 2493       | 4325           | 6818         | 69.8%  | 0.48 [0.36, 0.65]              |                                |
| **Total events** |            |                |              |        |                                |                                |
| 316               | 1370        |                |              |        |                                |                                |

Heterogeneity: Tau² = 0.18, Chi² = 38.19, df = 16 (P = 0.001); I² = 58%
Test for overall effect: Z = 4.86 (P < 0.00001)

| **2.2.2 Meetings abstracts or unpublished studies** |            |                |              |        |                                |                                |
|-----------------------------------------------------|------------|----------------|--------------|--------|--------------------------------|--------------------------------|
| Brinkley et al. 2010                               | 30         | 71             | 101          | 5.7%   | 0.53 [0.29, 0.98]              |                                |
| Grigoryan et al. 2015                              | 3          | 21             | 24           | 1.9%   | 0.42 [0.09, 1.96]              |                                |
| Lopes et al. 2010                                 | 6          | 46             | 52           | 3.5%   | 0.95 [0.34, 2.62]              |                                |
| Marchetti et al. 2012                              | 10         | 45             | 55           | 3.9%   | 0.36 [0.14, 0.89]              |                                |
| Shavit et al. 2018                                | 30         | 99             | 130          | 6.3%   | 1.07 [0.63, 1.84]              |                                |
| Turnasian et al. 2012                              | 21         | 34             | 55           | 4.5%   | 0.78 [0.35, 1.76]              |                                |
| Vukovic et al. 2016                               | 10         | 34             | 44           | 4.5%   | 1.44 [0.64, 3.25]              |                                |
| **Subtotal (95% CI)**                              | 350        | 746            | 1096         | 30.2%  | 0.76 [0.53, 1.10]              |                                |
| **Total events**                                   |            |                |              |        |                                |                                |
| 110                                               | 261         |                |              |        |                                |                                |

Heterogeneity: Tau² = 0.07; Chi² = 8.65, df = 6 (P = 0.19); I² = 31%
Test for overall effect: Z = 1.43 (P = 0.15)

| **Total (95% CI)**                                 | 2843       | 5071           | 100.0%       | 0.55   | [0.44, 0.70]                   |                                |
| **Total events**                                   | 426        | 1631           |              |        |                                |                                |

Heterogeneity: Tau² = 0.16; Chi² = 50.53, df = 23 (P = 0.0008); I² = 54%
Test for overall effect: Z = 4.85 (P < 0.00001)
Test for subgroup differences: Chi² = 3.72, df = 1 (P = 0.05), I² = 73.1%
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).

| Study or Subgroup | MRA | Control | Odds Ratio M-H, Random, 95% CI | Odds Ratio M-H, Random, 95% CI |
|-------------------|-----|---------|-------------------------------|-------------------------------|
|                   | Events | Total Events | Total Weight |                   |
| 2.2.1 Studies with high/serious risks of bias |       |           |               |                   |
| Bilotta et al. 2012 | 1 26 | 2 26 | 1.8% | 0.48 [0.04, 5.64] |
| Bosone et al. 2017 | 13 98 | 7 89 | 9.0% | 0.22 [0.12, 0.42] |
| Dabrowski et al. 2010 | 48 82 | 66 82 | 8.6% | 0.34 [0.17, 0.69] |
| Grigoryan et al. 2015 | 3 21 | 6 21 | 3.8% | 0.42 [0.09, 1.96] |
| Kim et al. 2009 | 5 48 | 69 48 | 1.4% | 0.04 [0.00, 0.76] |
| Letsas et al. 2009 | 2 6 | 26 6 | 3.1% | 0.77 [0.13, 4.51] |
| Lopes et al. 2010 | 6 46 | 15 110 | 6.3% | 0.95 [0.34, 2.62] |
| Marchetti et al. 2012 | 10 45 | 20 45 | 7.0% | 0.36 [0.14, 0.89] |
| Paziouda et al. 2003 | 0 21 | 12 75 | 1.4% | 0.12 [0.01, 2.08] |
| Preterius et al. 2012 | 38 147 | 40 147 | 10.0% | 0.93 [0.56, 1.57] |
| Shavit et al. 2018 | 30 99 | 51 177 | 9.9% | 1.07 [0.63, 1.84] |
| Simopoulos et al. 2015 | 40 132 | 90 200 | 10.5% | 0.53 [0.33, 0.85] |
| Tumasyan et al. 2012 | 21 34 | 68 101 | 7.8% | 0.78 [0.35, 1.76] |
| Vukicevic et al. 2016 | 10 34 | 43 192 | 7.7% | 1.44 [0.64, 3.25] |
| Williams et al. 2011 | 6 23 | 32 60 | 5.8% | 0.24 [0.08, 0.74] |
| Özaydin et al. 2010 | 4 69 | 46 200 | 6.0% | 0.21 [0.07, 0.60] |
| Subtotal (95% CI) | 890 1764 | 100.0% | 0.51 [0.36, 0.74] |

Total events 231 643
Heterogeneity: Tau² = 0.27; Chi² = 37.34, df = 15 (P = 0.001); I² = 60%
Test for overall effect: Z = 3.60 (P = 0.0003)

2.2.2 Studies with moderate or low risks of bias

| Study or Subgroup | MRA | Control | Odds Ratio M-H, Random, 95% CI | Odds Ratio M-H, Random, 95% CI |
|-------------------|-----|---------|-------------------------------|-------------------------------|
|                   | Events | Total Events | Total Weight |                   |
| Boldt et al. 2008 | 5 40 | 38 108 | 6.7% | 0.26 [0.10, 0.73] |
| Brinkley et al. 2010 | 30 71 | 58 100 | 13.3% | 0.53 [0.29, 0.98] |
| Cikes et al. 2018 | 57 615 | 55 592 | 20.3% | 1.00 [0.68, 1.47] |
| Disertori et al. 2010 | 39 92 | 70 705 | 18.9% | 0.67 [0.44, 1.03] |
| Gao et al. 2007 | 13 58 | 24 58 | 9.5% | 0.41 [0.18, 0.92] |
| Ito et al. 2013 | 22 55 | 64 106 | 12.2% | 0.44 [0.22, 0.85] |
| Swedberg et al. 2012 | 25 911 | 40 883 | 16.3% | 0.59 [0.36, 0.99] |
| Tsutsui et al. 2018 | 4 111 | 2 110 | 2.7% | 2.02 [0.36, 11.25] |
| Subtotal (95% CI) | 1953 3307 | 100.0% | 0.61 [0.45, 0.82] |

Total events 195 988
Heterogeneity: Tau² = 0.07; Chi² = 12.55, df = 7 (P = 0.08); I² = 44%
Test for overall effect: Z = 3.30 (P = 0.0010)

Test for subgroup differences: Chi² = 0.46, df = 1 (P = 0.50), I² = 0%
Figure S6. Impact of mineralocorticoid receptor antagonists (MRAs) on AF occurrence versus that of controls regarding the funding sources.

| Study or Subgroup                  | MRA Events | Control Events | Total Events | M-H, Random, 95% CI | Odds Ratio | Odds Ratio |
|------------------------------------|------------|----------------|--------------|----------------------|------------|------------|
| 2.2.1 Studies with industry fundings |            |                |              |                      |            |            |
| Cikes et al. 2018                  | 57         | 615            | 55 592       | 44.1%                | 1.00 [0.68, 1.47] |            |
| Kim et al. 2009                    | 0          | 0              | 5 69         | 4.6%                 | 0.04 [0.00, 0.76] |            |
| Swedberg et al. 2012               | 25         | 911            | 40 883       | 39.8%                | 0.59 [0.36, 0.99] |            |
| Tsutsui et al. 2018                | 4          | 111            | 2 110        | 11.5%                | 2.02 [0.36, 11.25] |            |
| Subtotal (95% CI)                  | 1642       | 1654           | 100%         | 0.76 [0.39, 1.47]    |            |            |
| Total events                       | 86         | 145            |              |                      |            |            |

Heterogeneity: Tau² = 0.22; Chi² = 7.66, df = 3 (P = 0.05); I² = 61%
Test for overall effect: Z = 0.82 (P = 0.41)

2.2.2 Studies with academic/institutional/government fundings

| Study or Subgroup                  | MRA Events | Control Events | Total Events | M-H, Random, 95% CI | Odds Ratio | Odds Ratio |
|------------------------------------|------------|----------------|--------------|----------------------|------------|------------|
| Bilota et al. 2012                 | 1          | 28             | 2 28         | 1.0%                 | 0.48 [0.04, 5.64] |            |
| Boldt et al. 2008                  | 5          | 40             | 38 108       | 4.0%                 | 0.26 [0.10, 0.73] |            |
| Bosone et al. 2017                 | 13         | 98             | 78 191       | 6.6%                 | 0.22 [0.12, 0.42] |            |
| Brinkley et al. 2010               | 30         | 71             | 58 100       | 6.9%                 | 0.53 [0.29, 0.98] |            |
| Dabrowski et al. 2010              | 48         | 82             | 66 82        | 6.1%                 | 0.34 [0.17, 0.69] |            |
| Disertori et al. 2010              | 39         | 92             | 70 1350      | 8.7%                 | 0.67 [0.44, 1.03] |            |
| Gao et al. 2007                    | 13         | 58             | 24 58        | 5.3%                 | 0.41 [0.18, 0.92] |            |
| Grigoryan et al. 2015              | 3          | 21             | 6 21         | 2.2%                 | 0.42 [0.09, 1.96] |            |
| Ito et al. 2013                    | 22         | 55             | 64 106       | 6.4%                 | 0.44 [0.22, 0.85] |            |
| Letsas et al. 2009                 | 2          | 6              | 26 66        | 1.7%                 | 0.77 [0.13, 4.51] |            |
| Lopes et al. 2010                  | 6          | 46             | 15 110       | 4.0%                 | 0.95 [0.34, 2.62] |            |
| Marchetti et al. 2012              | 10         | 45             | 20 45        | 4.6%                 | 0.36 [0.14, 0.89] |            |
| Paziaud et al. 2003                | 0          | 21             | 12 75        | 0.7%                 | 0.12 [0.01, 2.08] |            |
| Preterius et al. 2012              | 38         | 147            | 40 147       | 7.6%                 | 0.93 [0.56, 1.57] |            |
| Shavit et al. 2018                 | 30         | 99             | 51 177       | 7.6%                 | 1.07 [0.83, 1.38] |            |
| Simopoulos et al. 2015             | 40         | 132            | 90 200       | 8.3%                 | 0.53 [0.33, 0.85] |            |
| Turmasyan et al. 2012              | 21         | 34             | 68 101       | 5.3%                 | 0.78 [0.35, 1.76] |            |
| Vukicevic et al. 2016              | 10         | 34             | 43 192       | 5.3%                 | 1.44 [0.84, 2.55] |            |
| Williams et al. 2011               | 5          | 23             | 32 60        | 3.6%                 | 0.24 [0.08, 0.74] |            |
| Özaydin et al. 2010                | 4          | 69             | 46 200       | 3.8%                 | 0.21 [0.07, 0.60] |            |
| Subtotal (95% CI)                  | 1201       | 3417           | 100%         | 0.52 [0.40, 0.67]    |            |            |
| Total events                       | 340        | 1486           |              |                      |            |            |

Heterogeneity: Tau² = 0.15; Chi² = 38.06, df = 19 (P = 0.006); I² = 50%
Test for overall effect: Z = 5.02 (P < 0.00001)

Test for subgroup differences: Chi² = 1.08, df = 1 (P = 0.30), I² = 7.5%
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).

| Study or Subgroup | MRA Events | MRA Total | Control Events | Control Total | Odds Ratio M-H, Random, 95% CI |
|-------------------|------------|-----------|----------------|---------------|-------------------------------|
| **2.2.1 Spironolactone** | | | | | |
| Brinkley et al. 2010 | 30 | 71 | 58 | 100 | 5.7% | 0.53 [0.29, 0.98] |
| Cikes et al. 2018 | 57 | 615 | 55 | 592 | 7.4% | 1.00 [0.88, 1.17] |
| Dabrowski et al. 2010 | 48 | 82 | 66 | 82 | 5.1% | 0.34 [0.17, 0.69] |
| Gao et al. 2007 | 13 | 58 | 24 | 58 | 4.5% | 0.41 [0.18, 0.92] |
| Grigoryan et al. 2015 | 3 | 21 | 6 | 21 | 1.9% | 0.42 [0.09, 1.96] |
| Kim et al. 2009 | 0 | 5 | 48 | 69 | 0.6% | 0.04 [0.00, 0.76] |
| Letsas et al. 2009 | 2 | 6 | 26 | 66 | 1.5% | 0.77 [0.13, 4.51] |
| Lopes et al. 2010 | 6 | 46 | 15 | 110 | 3.5% | 0.95 [0.34, 2.62] |
| Paziaud et al. 2003 | 0 | 21 | 12 | 75 | 0.6% | 0.12 [0.01, 2.08] |
| Pretorius et al. 2012 | 38 | 147 | 40 | 147 | 6.4% | 0.93 [0.56, 1.57] |
| Shavit et al. 2018 | 30 | 99 | 51 | 177 | 6.3% | 1.07 [0.63, 1.84] |
| Turnasyan et al. 2012 | 21 | 34 | 68 | 101 | 4.5% | 0.78 [0.35, 1.76] |
| Vukicevic et al. 2016 | 10 | 34 | 43 | 192 | 4.5% | 1.44 [0.64, 3.25] |
| Williams et al. 2011 | 5 | 23 | 32 | 60 | 3.1% | 0.24 [0.08, 0.74] |
| Özyaydın et al. 2010 | 4 | 69 | 46 | 200 | 3.3% | 0.21 [0.07, 0.60] |
| **Subtotal (95% CI)** | 1331 | 2050 | 58.9% | 0.62 [0.45, 0.86] | |
| Total events | 287 | 590 | | | |
| Heterogeneity: Tau² = 0.19; Chi² = 31.10, df = 14 (P = 0.005); I² = 55%
Test for overall effect: Z = 2.90 (P = 0.004) |

| **2.2.2 Eplerenone** | | | | | |
| Ito et al. 2013 | 22 | 55 | 64 | 106 | 5.4% | 0.44 [0.22, 0.85] |
| Swedberg et al. 2012 | 25 | 911 | 40 | 883 | 6.5% | 0.59 [0.36, 0.99] |
| Tsutsumi et al. 2018 | 4 | 111 | 2 | 110 | 1.6% | 2.02 [0.36, 11.25] |
| **Subtotal (95% CI)** | 1077 | 1099 | 13.5% | 0.58 [0.35, 0.96] | |
| Total events | 51 | 106 | | | |
| Heterogeneity: Tau² = 0.06; Chi² = 2.72, df = 2 (P = 0.26); I² = 26%
Test for overall effect: Z = 2.11 (P = 0.04) |

| **2.2.3 Canrenone** | | | | | |
| Bilotta et al. 2012 | 1 | 28 | 2 | 28 | 6.9% | 0.48 [0.04, 5.64] |
| Bosone et al. 2017 | 13 | 98 | 75 | 191 | 5.5% | 0.22 [0.12, 0.42] |
| **Subtotal (95% CI)** | 126 | 219 | 6.3% | 0.23 [0.12, 0.44] | |
| Total events | 14 | 80 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.36, df = 1 (P = 0.55); I² = 0%
Test for overall effect: Z = 4.53 (P < 0.00001) |

| **2.2.4 MRA non specified** | | | | | |
| Boldt et al. 2008 | 5 | 40 | 38 | 108 | 3.5% | 0.26 [0.10, 0.73] |
| Díseri et al. 2010 | 39 | 92 | 70 | 1350 | 7.1% | 0.67 [0.44, 1.03] |
| Marchetti et al. 2012 | 10 | 45 | 20 | 45 | 3.9% | 0.36 [0.14, 0.89] |
| Simopoulos et al. 2015 | 40 | 132 | 90 | 200 | 6.8% | 0.53 [0.33, 0.85] |
| **Subtotal (95% CI)** | 309 | 1703 | 21.3% | 0.52 [0.37, 0.73] | |
| Total events | 94 | 855 | | | |
| Heterogeneity: Tau² = 0.02; Chi² = 3.68, df = 3 (P = 0.30); I² = 19%
Test for overall effect: Z = 3.85 (P = 0.0001) |

Total (95% CI) | 2843 | 5071 | 100.0% | 0.55 [0.44, 0.70] | |
Total events | 426 | 1631 | | | |
Heterogeneity: Tau² = 0.16; Chi² = 50.53, df = 23 (P = 0.0008); I² = 54%
Test for overall effect: Z = 4.85 (P < 0.00001)
Test for subgroup differences: Chi² = 7.50, df = 3 (P = 0.06), I² = 60.0%
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.

| Study or Subgroup | MRA | Control | Odds Ratio |
|-------------------|-----|---------|------------|
|                   | Events | Total | Events | Total | Weight | M-H, Random | 95% CI |
| 1.1.6 Newly Onset POAF | | | | | | | |
| Pretorius et al. 2012 | 38 | 147 | 40 | 147 | 23.1% | 0.93 [0.56, 1.57] |
| Shavit et al. 2019 | 30 | 99 | 51 | 177 | 22.7% | 1.07 [0.63, 1.84] |
| Simopoulos et al. 2015 | 40 | 132 | 90 | 200 | 24.3% | 0.53 [0.33, 0.85] |
| Vukicevic et al. 2016 | 10 | 34 | 43 | 192 | 17.0% | 1.44 [0.64, 3.25] |
| Özyaydın et al. 2010 | 4 | 69 | 46 | 200 | 12.9% | 0.21 [0.07, 0.60] |
| Subtotal (95% CI) | 481 | 916 | 100.0% | 0.74 [0.45, 1.23] |
| Total events | 122 | 270 |
| Heterogeneity: Tau² = 0.21; Chi² = 12.81, df = 4 (P = 0.01); I² = 69%
Test for overall effect: Z = 1.15 (P = 0.25) |
| 1.1.7 AF recurrence after electrical cardioversion | | | | | | | |
| Boldt et al. 2008 | 5 | 40 | 48 | 69 | 4.8% | 0.26 [0.10, 0.73] |
| McAlpine 2012 | 10 | 45 | 20 | 45 | 49.7% | 0.38 [0.14, 0.89] |
| Pazaud et al. 2003 | 0 | 21 | 12 | 75 | 5.1% | 0.12 [0.01, 2.08] |
| Subtotal (95% CI) | 110 | 297 | 100.0% | 0.27 [0.14, 0.51] |
| Total events | 15 | 118 |
| Heterogeneity: Tau² = 0.00; Chi² = 2.38, df = 3 (P = 0.50); I² = 0%
Test for overall effect: Z = 3.99 (P < 0.0001) |
| 1.1.8 AF recurrence after catheter ablation | | | | | | | |
| Ito et al. 2013 | 22 | 55 | 64 | 106 | 87.6% | 0.44 [0.22, 0.85] |
| Letsas et al. 2009 | 2 | 6 | 26 | 66 | 12.4% | 0.77 [0.13, 4.51] |
| Subtotal (95% CI) | 64 | 172 | 100.0% | 0.47 [0.25, 0.87] |
| Total events | 24 | 90 |
| Heterogeneity: Tau² = 0.00; Chi² = 0.34, df = 1 (P = 0.56); I² = 0%
Test for overall effect: Z = 2.38 (P = 0.02) |
Figure S9. Impact of mineralocorticoid receptor antagonists (MRAs) on AF occurrence versus that of controls in POAF and no-POAF studies.

| Study or Subgroup | MRA Events | Control Events | Total Events | Weight | Odds Ratio M-H, Random, 95% CI | Odd Ratio M-H, Random, 95% CI |
|-------------------|------------|----------------|--------------|--------|-------------------------------|-------------------------------|
| 2.2.1 No-POAF studies |
| Bilotta et al. 2012 | 1 | 28 | 28 | 1.1% | 0.48 [0.04, 5.64] | |
| Boldt et al. 2008 | 5 | 40 | 38 | 108 | 4.6% | 0.26 [0.10, 0.73] | |
| Bosone et al. 2017 | 13 | 98 | 78 | 191 | 7.6% | 0.22 [0.12, 0.42] | |
| Brinkley et al. 2010 | 30 | 71 | 58 | 100 | 8.0% | 0.53 [0.29, 0.98] | |
| Cikes et al. 2018 | 57 | 615 | 55 | 592 | 10.7% | 1.00 [0.68, 1.47] | |
| Dabrowski et al. 2010 | 48 | 82 | 66 | 82 | 7.1% | 0.34 [0.17, 0.69] | |
| Disertori et al. 2010 | 39 | 92 | 70 | 1350 | 10.2% | 0.67 [0.44, 1.03] | |
| Gao et al. 2007 | 13 | 58 | 24 | 58 | 6.1% | 0.41 [0.18, 0.92] | |
| Grigoryan et al. 2015 | 3 | 21 | 6 | 21 | 2.5% | 0.42 [0.09, 1.96] | |
| Ito et al. 2013 | 22 | 55 | 64 | 106 | 7.4% | 0.44 [0.22, 0.85] | |
| Kim et al. 2009 | 0 | 5 | 5 | 48 | 69 | 0.8% | 0.04 [0.00, 0.76] | |
| Letsas et al. 2009 | 2 | 6 | 26 | 66 | 2.0% | 0.77 [0.13, 4.51] | |
| Lopes et al. 2010 | 6 | 46 | 15 | 110 | 4.6% | 0.95 [0.34, 2.62] | |
| Marchetti et al. 2012 | 10 | 45 | 20 | 45 | 5.3% | 0.36 [0.14, 0.89] | |
| Paziaud et al. 2003 | 0 | 21 | 12 | 75 | 0.8% | 0.12 [0.01, 2.08] | |
| Swedberg et al. 2012 | 25 | 911 | 40 | 883 | 9.2% | 0.59 [0.36, 0.99] | |
| Tsutsui et al. 2018 | 4 | 111 | 2 | 110 | 2.1% | 2.02 [0.36, 11.25] | |
| Turmasyan et al. 2012 | 21 | 34 | 68 | 101 | 6.1% | 0.78 [0.35, 1.76] | |
| Williams et al. 2011 | 5 | 23 | 32 | 60 | 4.1% | 0.24 [0.08, 0.74] | |
| Subtotal (95% CI) | 2362 | 4155 | 100.0% | 0.50 [0.38, 0.65] | |

Total events: 304 | 1361

Heterogeneity: Tau² = 0.14; Chi² = 33.69, df = 18 (P = 0.01); I² = 47%

Test for overall effect: Z = 5.12 (P < 0.00001)

2.2.2 POAF studies

| Study or Subgroup | MRA Events | Control Events | Total Events | Weight | Odds Ratio M-H, Random, 95% CI | Odd Ratio M-H, Random, 95% CI |
|-------------------|------------|----------------|--------------|--------|-------------------------------|-------------------------------|
| Pretorius et al. 2012 | 38 | 147 | 40 | 147 | 23.1% | 0.93 [0.56, 1.57] | |
| Shavit et al. 2018 | 30 | 99 | 51 | 177 | 22.7% | 1.07 [0.63, 1.84] | |
| Simopoulos et al. 2015 | 40 | 132 | 90 | 200 | 24.3% | 0.53 [0.33, 0.85] | |
| Vukicevic et al. 2016 | 10 | 34 | 43 | 192 | 17.0% | 1.44 [0.64, 3.25] | |
| Özyaydın et al. 2010 | 4 | 69 | 46 | 200 | 12.9% | 0.21 [0.07, 0.60] | |
| Subtotal (95% CI) | 481 | 916 | 100.0% | 0.74 [0.45, 1.23] | |

Total events: 122 | 270

Heterogeneity: Tau² = 0.21; Chi² = 81.81, df = 4 (P = 0.01); I² = 69%

Test for overall effect: Z = 1.15 (P = 0.25)

Test for subgroup differences: Chi² = 1.93, df = 1 (P = 0.16); I² = 48.1%
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.

| Study or Subgroup | MRA Events | Control Events | Total Events | Weight | Odds Ratio M-H, Fixed, 95% CI | Odds Ratio M-H, Fixed, 95% CI |
|-------------------|------------|----------------|--------------|--------|-------------------------------|-------------------------------|
| **2.2.1 Randomized placebo-controlled trials** |
| Cikes et al. 2018 | 57         | 615            | 55           | 592    | 0.89%                         | 1.00 [0.68, 1.47]             |
| Gao et al. 2007  | 13         | 58             | 24           | 58     | 3.6%                          | 0.41 [0.18, 0.92]             |
| Grigoryan et al. 2015 | 3          | 21             | 6            | 21     | 1.0%                          | 0.42 [0.09, 1.96]             |
| Pretorius et al. 2012 | 38          | 147            | 40           | 147    | 5.7%                          | 0.93 [0.56, 1.57]             |
| Swedberg et al. 2012 | 25         | 911            | 40           | 883    | 7.6%                          | 0.58 [0.36, 0.99]             |
| Tsutsui et al. 2018 | 4           | 111            | 2            | 110    | 0.4%                          | 2.02 [0.36, 11.25]            |
| **Subtotal (95% CI)** | **1863** | **1811**      | **1811**     | **28.2%** | **0.79 [0.62, 1.01]**      |                               |
| Total events | 140        | 167            |              |        |                               |                               |
| Heterogeneity: Chi² = 7.31, df = 5 (P = 0.20); I² = 32% |
| Test for overall effect: Z = 1.87 (P = 0.06) |

| **2.2.2 Randomized controlled trials** |
| Biotta et al. 2012 | 1           | 28             | 2            | 28     | 0.4%                          | 0.48 [0.04, 5.64]             |
| Bosone et al. 2017 | 13          | 98             | 76           | 191    | 8.9%                          | 0.22 [0.12, 0.42]             |
| Dabrowski et al. 2010 | 48         | 82             | 66           | 82     | 5.3%                          | 0.34 [0.17, 0.69]             |
| Marchetti et al. 2012 | 10          | 45             | 20           | 45     | 3.0%                          | 0.36 [0.14, 0.89]             |
| Tumayan et al. 2012 | 21          | 34             | 68           | 101    | 2.5%                          | 0.78 [0.35, 1.76]             |
| **Subtotal (95% CI)** | **327** | **447**        |              | **26.1%** | **0.35 [0.24, 0.50]**      |                               |
| Total events | 93         | 234            |              |        |                               |                               |
| Heterogeneity: Chi² = 5.80, df = 4 (P = 0.21); I² = 31% |
| Test for overall effect: Z = 3.70 (P < 0.00001) |

| **2.2.3 Prospective observational studies** |
| Boldt et al. 2008 | 5           | 40             | 36           | 108    | 3.5%                          | 0.26 [0.10, 0.73]             |
| Disertori et al. 2010 | 39         | 92             | 707          | 1350   | 10.0%                         | 0.67 [0.44, 1.03]             |
| Kim et al. 2009 | 0           | 5              | 48           | 69     | 1.4%                          | 0.04 [0.00, 0.76]             |
| Letsas et al. 2009 | 2           | 6              | 26           | 66     | 0.6%                          | 0.77 [0.13, 4.51]             |
| Shavit et al. 2018 | 30          | 99             | 51           | 177    | 4.9%                          | 1.07 [0.63, 1.84]             |
| Özaydin et al. 2010 | 4           | 69             | 46           | 200    | 4.3%                          | 0.21 [0.07, 0.60]             |
| **Subtotal (95% CI)** | **311** | **1970**       |              | **24.7%** | **0.58 [0.44, 0.77]**       |                               |
| Total events | 80         | 916            |              |        |                               |                               |
| Heterogeneity: Chi² = 14.70, df = 5 (P = 0.01); I² = 66% |
| Test for overall effect: Z = 3.72 (P = 0.00002) |

| **2.2.4 Retrospective observational studies** |
| Brinkley et al. 2010 | 30          | 71             | 56           | 100    | 5.4%                          | 0.53 [0.29, 0.98]             |
| Ito et al. 2013 | 22          | 55             | 64           | 106    | 5.1%                          | 0.44 [0.22, 0.85]             |
| Lopes et al. 2010 | 6           | 46             | 15           | 110    | 1.5%                          | 0.95 [0.34, 2.62]             |
| Paziau et al. 2003 | 0           | 21             | 12           | 75     | 1.1%                          | 0.12 [0.01, 2.08]             |
| Simopoulos et al. 2015 | 40         | 132            | 90           | 200    | 9.6%                          | 0.53 [0.33, 0.85]             |
| Vukicevic et al. 2016 | 10          | 34             | 43           | 192    | 1.8%                          | 1.44 [0.64, 3.25]             |
| Williams et al. 2011 | 5           | 23             | 32           | 60     | 2.7%                          | 0.24 [0.08, 0.74]             |
| **Subtotal (95% CI)** | **382** | **843**        |              | **27.1%** | **0.55 [0.42, 0.73]**       |                               |
| Total events | 113        | 314            |              |        |                               |                               |
| Heterogeneity: Chi² = 10.19, df = 6 (P = 0.12); I² = 41% |
| Test for overall effect: Z = 4.22 (P < 0.0001) |

| **Total (95% CI)** | **2843** | **5071**       | **100.0%** | **0.59 [0.51, 0.67]**       |                               |
| Total events | 426        | 1631           |              |        |                               |                               |
| Heterogeneity: Chi² = 50.53, df = 23 (P = 0.0008); I² = 54% |
| Test for overall effect: Z = 7.43 (P < 0.00001) |
| Test for subgroup differences: Chi² = 13.97, df = 3 (P = 0.003), I² = 78.5% |
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 inpatients 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, İbişim 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, Adamyk 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 spiro lactone 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.