The Effects of Mineralocorticoid Receptor Antagonists on the Risk of Sudden Cardiac Death in Patients with Left Ventricular Systolic Dysfunction: A Meta-analysis of Randomized Controlled Trials

Bapoje et al: Mineralocorticoid Receptor Antagonists and Sudden Cardiac Death

Srinivas R. Bapoje, MD, MPH1, 2, 6
Amit Bahia, MD, MPH1, 2, 6
John E. Hokanson, MPH, PhD4
Pamela N. Peterson, MD, MSPH1, 2, 3
Paul A. Heidenreich, MD, MS5
JoAnn Lindenfeld, MD2
Larry A. Allen, MD, MHS2, 3
Frederick A. Masoudi, MD, MSPH2, 3

1Department of Medicine, Denver Health and Hospital Authority, Denver Colorado; 2Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, Colorado; 3Colorado Cardiovascular Outcomes (C-COR) Consortium, Denver, Colorado; 4Department of Epidemiology, Colorado School of Public Health, University of Colorado Anschutz Medical Campus, Aurora, Colorado; 5Department of Medicine, VA Palo Alto Healthcare System, Palo Alto, California; 6Department of Cardiology, University of Arkansas for Medical Sciences, Little Rock, Arkansas

Correspondence to:
Srinivas R. Bapoje, MD, MPH
4301 West Markham Street, Slot 532
Little Rock, AR 72205
Email srbapoje@uams.edu
Phone: (501) 686-7882
Fax: (501)-686-6439

DOI: 10.1161/CIRCHEARTFAILURE.112.000003

Journal Subject Code: 110
Abstract

Background—Sudden cardiac death (SCD) is a leading cause of mortality in patients with left ventricular systolic dysfunction (LVSD). Mineralocorticoid receptor antagonists (MRAs) may attenuate this risk. The objective of this meta-analysis was to assess the impact of MRAs on SCD in patients with LVSD.

Methods and Results—We systematically searched PubMed, EMBASE, Cochrane and other databases through March 30th 2012 without language restrictions. We included trials that enrolled patients with left ventricular ejection fraction of ≤45%, randomized subjects to MRAs vs. control, and reported outcomes on SCD, total and cardiovascular mortality. Eight published trials that enrolled 11,875 patients met inclusion criteria. Of these, six reported data on SCD and cardiovascular mortality, and seven reported data on total mortality. No heterogeneity was observed among the trials. Patients treated with MRAs had 23% lower odds of experiencing SCD compared with controls, OR = 0.77 [95% CI 0.66-0.89; p = 0.001]. Similar reductions were observed in cardiovascular [OR 0.75; 95% CI 0.68-0.84; p < 0.001], and total mortality [OR = 0.74; 95% CI 0.63-0.86; p < 0.001]. Although publication bias was observed, the results did not change after a trim and fill test suggesting that the impact of this bias was likely insignificant.

Conclusions—MRAs reduce the risk of SCD in patients with LVSD. Comparative effectiveness studies of MRAs on SCD in usual care as well as studies evaluating the efficacy of other therapies to prevent SCD in patients receiving optimal MRA use are needed to guide clinical decision-making.

Key Words: sudden cardiac death, mineralocorticoid receptor antagonists, left ventricular systolic dysfunction, meta-analysis
Sudden cardiac death (SCD) is an important cause of mortality in patients with left ventricular systolic dysfunction (LVSD). Patients with LVSD and New York Heart Association (NYHA) class III heart failure symptoms have an annual rate of SCD of 4.6%; this rate approaches 6% among those with the most severe symptoms. Because the index sudden cardiac arrest event is usually fatal, the use of implantable cardioverter-defibrillators (ICDs) is recommended for the primary prevention of SCD for selected patients with LVSD. ICD therapy is expensive, however, and many patients clinically eligible for primary prevention ICD therapy do not receive appropriate therapy. With a rising prevalence of heart failure, the burden of morbidity and mortality from SCD is expected to increase, and will present ever-increasing clinical and financial challenges in the care of patients with LVSD.

Abnormal neurohumoral signaling by the renin-angiotensin-aldosterone signaling (RAAS) contributes to the pathophysiologic basis of SCD in patients with LVSD. In animal models, suppression of the RAAS system by eplerenone attenuates heart failure-related ventricular electrical remodeling and tachyarrhythmia vulnerability. Some clinical trials evaluating the blockade of RAAS in patients with LVSD have shown reductions in mortality from SCD; however, other studies have failed to reproduce these results. The use of mineralocorticoid receptor antagonists (MRAs) such as spironolactone and eplerenone in the prevention of SCD in patients with LVSD presents an attractive adjunctive therapy given the issues of cost and access to ICD therapy, the limited effectiveness of and side effects profiles of antiarrhythmic drugs, and the incomplete neurohumoral suppression by angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB). While meta-analyses have explored the effect of ACEI on SCD, similar analyses assessing at the effect of MRAs on SCD in patients with LVSD have been lacking. Accordingly, we conducted a meta-
analysis of existing trials of MRAs used in the setting of LVSD with the hypothesis that MRAs decrease the risk of SCD in this patient population.

Methods

We performed a systematic review and meta-analysis of randomized controlled trials of MRAs in patients with LVSD according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines 17.

Data Sources

We conducted a highly sensitive and a comprehensive systematic search of major scientific databases including PubMed (MEDLINE), EMBASE, Cochrane, US Food and Drug Administration and clinical trials databases (clinicaltrials.gov, controlled-trials.com and clinicaltrialsregister.eu) without any language restrictions through March 30th 2012 for randomized controlled trials using the key words of “aldosterone antagonists, spironolactone, Aldactone ®, eplerenone, Inspra ®, canrenone, canrenoate, heart failure, systolic failure, systolic dysfunction, congestive heart failure and cardiovascular disease” (see Appendix  for full search strategy). We also searched abstracts of major US cardiovascular medicine conference proceedings (AHA and ACC), references of primary journal articles and systematic reviews identified by the initial search. We also contacted experts in the field to identify other unpublished or published research relevant to our study. We made an attempt to obtain unreported or missing data from the corresponding authors if the trials met our inclusion criteria.
Study Selection

We included randomized controlled trials that 1) enrolled adult patients with symptomatic or asymptomatic heart failure with LVSD (defined as LVEF of \( \leq 45\% \)), 2) assigned patients to MRA therapy versus placebo or control, 3) reported data on SCD, or total and cardiovascular (CV) mortality, 4) had a study duration and a follow up of greater than or equal to two months, and 5) had at least 25 patients in both the arms. Trials in patients with recent myocardial infarction were included in the study if randomization occurred at least three days after infarction to limit the potential bias from ischemia-induced malignant ventricular arrhythmias.

We studied the primary outcomes of SCD, and secondary outcomes of total and CV mortality to evaluate the pooled benefit of MRAs in patients with LVSD. We assessed the definition of SCD used by the individual studies. Most studies used the SCD definition from the ACC/AHA/European Society of Cardiology (ESC) 2006 guidelines for management of patients with ventricular arrhythmias and prevention of SCD \(^{18}\), as “death from an unexpected circulatory arrest, usually due to a cardiac arrhythmia, occurring within an hour of the onset of symptoms,” and CV mortality was defined as death from any cardiovascular cause.

Data Extraction and Quality Assessment

Two independent reviewers (SRB and AB) screened the abstracts of all the citations obtained by the initial search in a standardized and un-blinded manner. Full texts of studies that met our inclusion criteria were then retrieved for secondary data extraction using a standardized form that included baseline patient characteristics; study design; quality, as assessed by the Cochrane Collaboration’s Risk of Bias Tool \(^{19}\); MRAs used; and primary and secondary outcomes. Multiple reports of the same study were linked together by identifying author names, dates and
duration of the study, location and setting, details of intervention and numbers of participants. Data were subsequently extracted from each report separately and duplicate data were discarded. The reviewers verified the accuracy and completeness of data. If there was any uncertainty in the accuracy, we contacted the corresponding authors to prevent bias from duplication of data. We also calculated the numbers needed to treat (NNT) to prevent one SCD for each study. The studies that met our inclusion criteria were evaluated for the risk of bias using a six-domain tool (sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting and other sources of bias) suggested by the Cochrane collaborators group. The corresponding authors were contacted for any missing data elements. Disagreement between the two reviewers was resolved by consensus and secondary review from one of the other investigators.

**Data Synthesis and Analysis**

We calculated the summary odds ratio (OR) and 95% CI for the outcome variables of interest by using DerSimonian and Laird random effects model. We decided, a priori, to use a random effects model for the primary analysis as we anticipated heterogeneity between the trials. Clinical heterogeneity between the trials was explored by using subgroup analysis by random effects model based on definition of SCD (AHA/ESC guidelines vs. other definition), MRA agent used (eplerenone vs. spironolactone and canrenone), and the degree of LVSD (EF ≤ 35% vs. ≤ 45%). Because canrenone is an active metabolite of spironolactone, we combined trials using spironolactone and canrenone for the MRA subgroup analysis. We conducted a meta-regression to adjust for study-level differences in rates of evidence based therapies that might influence SCD risk, using ACEI/ARB, β- blockers, statins, anti-arrhythmic agents and ICDs as
covariates. The overall adverse event rate of MRAs varied from 55% to 82% between groups with inconsistent reporting and significant heterogeneity in defining them in each trial due to which we did not assess its impact. We performed a sensitivity analysis to verify the strength of our results by removing each trial from the analysis and recalculating the results to determine whether the pooled summary estimate was affected by a particular trial. Statistical heterogeneity was measured by calculating the Cochran $Q$ statistic, which informs about the presence of heterogeneity and the $I^2$ statistic, which quantifies the degree of heterogeneity between trials. A priori, we defined significant heterogeneity between trials as an $I^2$ value of greater than 50%. We assessed for evidence of publication bias by constructing a funnel plot and Eggers test. A two-sided p value of $<0.05$ was considered statistically significant for all analysis. Statistical analysis was performed using Comprehensive Meta-analysis® Version 2 (Biostat, Englewood NJ 2005).

Results

Our initial search strategy yielded 1887 studies (Figure 1, PRISMA flow diagram). Of these, eight RCTs enrolling a total of 11,875 patients met our inclusion criteria. The study characteristics of all the trials are summarized in Tables 1-4. Six trials enrolling 11,654 patients reported data on SCD and CV mortality and seven trials enrolling 11,826 patients reported data on total mortality. Two trials met criteria for poor methodological quality and the other six trials met criteria for good quality (see Appendix, Table 1 for quality assessment data for the trials). The EPHESUS trial accounted for more than half of the patients for this meta-analysis. The etiology of LVSD in all the trials was a combination of both ischemic and non-ischemic causes except for EPHESUS that selectively enrolled patients after a
myocardial infarction. The EMPHASIS-HF trial enrolled patients with LVSD with mild heart failure symptoms, while RALES enrolled patients with severe symptoms. In all the trials that reported data on SCD, this outcome was considered a secondary outcome. The dropout rate varied from 0% to as high as 35%. Half of the trials that reported data on SCD used the SCD definition from the 2006 ACC/AHA/ESC guidelines (Table 2)\(^{18}\). Adherence with MRAs in the intervention groups when measured varied from 74% to 95%. All the trials reported greater than 80% usage of ACEI and/or ARB among all the groups. The usage of β blockers varied from 11% to 87%. Statin, antiarrhythmic drug and ICD usage was reported inconsistently.

**Sudden Cardiac Death, CV mortality and Total mortality**

There were a total of 709 SCDs among 11,654 patients (6%), 310 of which occurred in patients treated with MRAs (2.6%, Figure 2). Overall, patients with LVSD who were treated with MRAs had 23% lower odds of SCD compared with controls (OR = 0.77; 95% CI 0.66-0.89; \(p = 0.001\)). The number needed to treat to prevent one SCD among trials ranged from 22 to 88, varying by duration of follow up (Table 3). No significant heterogeneity was observed among the trials (\(Q = 0.67; I^2 = 0.00; p = 0.98\)). Similar reductions in CV mortality [OR 0.75; 95 % CI 0.68-0.84; \(p < 0.001\)] and total mortality [OR = 0.74; 95% CI 0.63-0.86; \(p < 0.001\)] were observed in the pooled analysis among patients treated with MRAs compared to controls without any significant heterogeneity observed between the trials for both the outcomes [\(Q = 4.36, p = 0.49; I^2=0\) for CV mortality, and \(Q = 6.74 p = 0.15; I^2 = 40.7\) for total mortality].

A sensitivity analysis performed by removing each of the trials from the model and re-computing the summary odds ratio found similar point estimates. In particular, the results were
unchanged when EPHESUS, the largest study, was removed from the model OR = 0.74 [95% CI 0.59- 0.93; p = 0.01].

We observed publication bias for all the outcomes with an Eggers test two tailed p value of 0.01 for SCD and a visually asymmetrical funnel plot (Appendix, Figure 1). We calculated that the number of missing studies needed to raise the p-value for significance above 0.05 to be nine. We also performed a trim and fill test to adjust for the smaller and less precise studies to the right of mean and found an unchanged point estimate for SCD with an OR of 0.77 [95% CI 0.66-0.90].

Sub-group analysis for SCD

The overall result did not change substantially when we limited the study to trials using the 2006 ACC/AHA/ESC practice guidelines on definition of SCD, \(^{11,12,25}\), that enrolled 4506 patients compared to trials using other definitions, that enrolled 7148 patients, \(^{24,26,27}\), with OR 0.75 [95% CI 0.60- 0.94, p= 0.01] vs. OR = 0.78 [95% CI 0.63-0.96, p = 0.02], respectively. We also found that the SCD risk reduction with MRAs was similar for trials that enrolled 4449 patients with more severe LVSD with an EF \(\leq 35\%\) \(^{11,12,27}\) with OR = 0.75 [95% CI 0.60-0.94, p= 0.01] compared to OR = 0.78 [95% CI 0.63- 0.96, p= 0.02] for trials that enrolled 7205 patients with an EF of \(\leq 45\%\) (24,25,26). The reduction in SCD risk in trials that used eplerenone (n= 9369, summary OR 0.79 (95% CI 0.66-0.94, p = 0.01) was similar to that in trials that used canrenone or spironolactone (n=2285, summary OR 0.71 (95% CI 0.53- 0.96, p = 0.02).
Meta-regression of evidence based therapies for SCD

Use of some medical therapies such as anti-arrhythmic drugs, statins and ICD was reported inconsistently. All trials reported greater than 80% use of ACEI/ARB in both arms. Thus, we did not explore the effects of these agents on the results. Because there were substantial study-level differences in rates of β- blocker use between the groups, we conducted a meta-regression modeling of the log-odds of SCD against β- blocker usage of usage of ≥75% or < 75%. There was no significant change in the odds of SCD between trials that reported ≥ 75% baseline usage of β- blockers compared to trials that reported < 75% usage of β- blockers (p = 0.65).

Discussion

We found that in randomized controlled trials, patients with LVSD treated with MRAs had 23% lower odds of SCD compared with controls. Similar risk reductions were observed in total and CV mortality. The finding was robust, with consistent results in a range of sensitivity analyses. The benefits of MRAs were similar in patient subgroups with different LVSD inclusion criteria, in patients randomized to spironolactone or eplerenone, and across studies that used standard and non-standard definitions of SCD. A meta-regression modeled on beta-blocker usage did not show any difference in mortality benefit among trials with greater or less than 75% usage of beta-blockers.

The substantial reduction in the risk of SCD with MRAs therapy in patients with LVSD identified in this study has important implications. First, few of the patients enrolled in the trials of MRA for systolic heart failure were treated with ICDs, providing the ability to ascertain the independent benefits of MRA on this important outcome. Second, the effect of MRAs on SCD is important given the fact that MRAs are a particularly underutilized class of medications in
patients with heart failure\textsuperscript{30} and have a high potential impact on reduction of mortality among evidence based therapies for heart failure with optimal implementation \textsuperscript{31}. Third, the benefits of eplerenone on sudden cardiac death were similar to those of spironolactone. Eplerenone, with its selective effect on the mineralocorticoid receptor, has fewer side effects and, by extension, the potential for better adherence compared with spironolactone \textsuperscript{32, 33}. Finally, we found a similar effect in the sub group of patients with milder LVSD (\(\leq 45\%\), as opposed to \(\leq 35\%\)). Because the sample size of patients with milder LVSD was small, it is not possible to draw definitive conclusions of benefit. However, because such patients are at a greater risk for SCD than patients with normal LV systolic function and such patients are not typically considered candidates for primary prevention ICD therapy, aldosterone antagonists may represent an attractive therapeutic option in such patients. Ultimately, the trials of aldosterone antagonists in this patient population will provide more definitive insight into this hypothesis-generating finding.

The therapeutic effect of SCD prevention with MRAs is postulated to accrue from a variety of mechanisms. First, by means of an enhanced and sustained suppression of the RAAS system, MRAs potentiate the effect of ACE-I and ARBs on ventricular remodeling in HF and post-MI patients \textsuperscript{34}. MRAs directly suppress the arrhythmogenic effects of aldosterone at multiple levels. At the tissue level, the blockade of the mineralocorticoid receptor limits potassium and magnesium loss, myocardial fibrosis and hypertrophy, and stimulation of the central adrenergic system \textsuperscript{35, 36} and \textsuperscript{37}. The reduced electrical remodeling lowers the propensity for ventricular arrhythmias. At the cellular level, MRAs suppress the combined effect of aldosterone on select calcium and potassium currents that prolongs the ventricular action potential duration and lowers the threshold for ventricular arrhythmias \textsuperscript{38, 39}. Also, MRAs reduce the release of norepinephrine from sympathetic nerve terminals through enhanced parasympathetic activity and
promotes its direct reuptake into the myocyte reducing ventricular arrhythmias. Finally, the MRAs prevent elevated cortisol from activating mineralocorticoid receptors resulting in deceased substrate for arrhythmias and SCD.

Our results are particularly relevant in light of the trials of ICD therapy as a means of reducing the risk of SCD in patients with LVSD. The SCD-HeFT trial that randomized patients with LVSD with EF of ≤ 35% in NYHA class II or III heart failure to antiarrhythmic therapy and ICD also found a 23% risk reduction in mortality among patients treated with single lead ICD. None of the treated groups received MRA therapy, however. The COMPANION trial, which randomized 1520 patients with LVEF ≤ 35% in NYHA class III or IV heart failure on ‘optimal medical therapy’ to no Cardiac Resynchronization Therapy (CRT) and CRT with and without defibrillator, found a 20% risk reduction in cardiovascular death in both CRT with and without defibrillator arms. Only 50% of patients in each arm were treated with MRAs and, furthermore, there was significant cross over to the device arms because of arrhythmia or heart failure. Consistent with our hypothesis, as the medical therapy in the trials of ICDs was optimized from MADIT I to SCD-HeFT, the degree of superiority of the ICD over conventional therapy declined suggesting that mortality in both groups in these trials may have differed because of changes of contemporary background medical therapy and enrollment of patients with non-ischemic cardiomyopathy in SCD-HeFT trial. Conversely, because aldosterone antagonists and defibrillators address SCD through different therapeutic pathways, it is possible that combined treatment with ICD and MRAs could offer even greater effectiveness to the highest risk patients. Given the low rates of use of aldosterone antagonists in the trials that form the basis of guideline recommendations for primary prevention ICD use, and given that the cost effectiveness of ICD therapy is highly sensitive to the baseline risk of SCD, it would be
informative to understand the effectiveness and cost-effectiveness of ICDs in patients optimally treated with background medical therapy that includes an aldosterone antagonist. Finally, every attempt should be made to ensure that patients with LVSD who refuse an ICD or are otherwise not a candidate for this therapy receive an MRA unless contraindicated.

Our results raise important direction for future research. As the current guidelines for primary prevention with ICD therapy are based on studies that enrolled patients with almost no background medical therapy, it is imperative to quantify the incremental benefit of ICD therapy in patients on optimal evidence-based heart failure therapy, including MRAs among eligible patients. Additionally, it would be informative to better understand the efficacy and cost effectiveness of ICD therapy in patients treated with MRAs, particularly in the context of an anticipated increase in the overall prevalence of heart failure.

Certain issues should be considered in the interpretation of our results. First, it is possible but less likely that we did not identify important unpublished randomized trials evaluating the clinical outcomes of MRAs in patients with LVSD. We implemented a rigorous and comprehensive search strategy to identify candidate studies and doubt that we could have missed enough studies to affect our final outcome. Second, trials differed in how they defined SCD. Our finding that the effect size was same no matter what definition of SCD was chosen runs counter to the concern that the use of non-standard definitions of SCD may falsely increase the incidence of SCD. If this were indeed the case, we would have observed smaller risk reduction in groups that used a non-standard definition of SCD. As we did not identify differences in SCD rates on sub-group analysis we infer that the use of non-standard definitions did not have a significant effect on our conclusions. Third, we identified publication bias in that most of the included studies reported results in favor of MRAs. The methodological standards for meta-analysis.
support the inclusion of all available studies that fulfill the pre-specified inclusion criteria to prevent publication bias as we did in this study. While this bias could have influenced our results we believe it is highly unlikely that we failed to identify the number of RCTs that would be necessary to negate our findings. Moreover, the results of the trim and fill test suggest that the publication bias could have resulted from the inclusion of studies with high standard error of mean. Finally, we did not have access to patient level data regarding the use of other therapies. Accordingly, we could not assess the interaction between these therapies with respect to their impact on SCD prevention. We did, however, conduct a meta-regression modeling the odds of SCD against study level β- blocker usage to account for the heterogeneity in rates of β-blocker use between the included studies and did not find any difference between the groups.

In conclusion, our study provides evidence that MRAs prevent SCD in a broad range of patients with LVSD enrolled in clinical trials. These results support efforts to enhance the use of MRAs in eligible patients with LVSD in community practice, particularly those patients with LVSD who decline or are otherwise ineligible for ICD therapy. Furthermore, these results have implications for studies of other therapies intended to address the risk of SCD in this patient population. Specifically, future studies of interventions to mitigate SCD risk in patients with LVSD should be performed in patients receiving medical therapy that includes MRAs. Furthermore, studies to assess the incremental benefits of ICD in the context of optimal medical therapy would be informative to the therapeutic guidelines for the treatment of heart failure.
Acknowledgements

All the authors were involved in the design of the study and preparation of the manuscript. Drs. Bapoje and Bahia had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Sources of Funding

There was no role for any external funding source in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. Colorado Clinical and Translational Sciences Institute was involved in the assistance with the design of this study.

Disclosures

None.

References


Table 1. Baseline characteristics of all trials

<table>
<thead>
<tr>
<th>Study, year</th>
<th>MRAs treatment group</th>
<th>Control group</th>
<th>Inclusion EF*, %</th>
<th>Inclusion creatinine, μmol/L</th>
<th>Study subjects</th>
<th>NYHA† class</th>
<th>Primary outcome, Effect of MRAS on</th>
<th>Mean EF in MRAs group, % ± SD ‡</th>
<th>Mean EF in control group, % ± SD ‡</th>
<th>Study center type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akbulut et al, 2003</td>
<td>35</td>
<td>70</td>
<td>≤ 35</td>
<td>≤ 176.8</td>
<td>Chronic CHF</td>
<td>3</td>
<td>QT dispersion</td>
<td>27.2 ± 2</td>
<td>27.7 ± 3</td>
<td>Single</td>
</tr>
<tr>
<td>AREA-IN-CHF, 2009</td>
<td>231</td>
<td>236</td>
<td>≤ 45</td>
<td>≤ 221</td>
<td>Chronic CHF</td>
<td>2</td>
<td>LV remodeling and function</td>
<td>39.9 ± 8.6</td>
<td>39.7 ± 8.6</td>
<td>Multi</td>
</tr>
<tr>
<td>Cicoira et al, 2002</td>
<td>54</td>
<td>52</td>
<td>≤ 45</td>
<td>≤ 150.2</td>
<td>Chronic CHF</td>
<td>1-3</td>
<td>LV function and exercise tolerance</td>
<td>33 ± 7</td>
<td>34 ± 7</td>
<td>Single</td>
</tr>
<tr>
<td>RALES, 1999</td>
<td>822</td>
<td>841</td>
<td>≤ 35</td>
<td>≤ 221</td>
<td>Chronic CHF</td>
<td>2-4</td>
<td>Total mortality</td>
<td>25.6 ± 6.7</td>
<td>25.2 ± 6.8</td>
<td>Multi</td>
</tr>
<tr>
<td>EPHESUS, 2003</td>
<td>3319</td>
<td>3313</td>
<td>≤ 40</td>
<td>≤ 221</td>
<td>Post-MI † with LVSD ‡</td>
<td>NR</td>
<td>Total &amp; CV †† mortality, hospitalization for CV causes</td>
<td>33 ± 6</td>
<td>33 ± 6</td>
<td>Multi</td>
</tr>
<tr>
<td>EMPHASIS-HF, 2011</td>
<td>1364</td>
<td>1373</td>
<td>≤ 35</td>
<td>≤ 33 ± 7</td>
<td>Chronic CHF</td>
<td>2</td>
<td>Composite of death and hospitalization for CHF</td>
<td>26.2 ± 4.6</td>
<td>26.1 ± 4.7</td>
<td>Multi</td>
</tr>
<tr>
<td>Skvortsov et al, 2007</td>
<td>19</td>
<td>30</td>
<td>≤ 35</td>
<td>≤ 150.2</td>
<td>Chronic CHF</td>
<td>2-4</td>
<td>LV remodeling, safety and clinico-funct. status</td>
<td>27.3 ± 7.5</td>
<td>31.2 ± 3.5</td>
<td>Single</td>
</tr>
<tr>
<td>Gao et al, 2007</td>
<td>58</td>
<td>58</td>
<td>&lt; 45</td>
<td>≤ 221</td>
<td>Chronic CHF</td>
<td>2-4</td>
<td>Mg †† level and arrhythmias</td>
<td>42 ± 11</td>
<td>43 ± 10</td>
<td>Single</td>
</tr>
</tbody>
</table>

* ejection fraction; †New York heart association; ‡ standard deviation; § congestive heart failure; || left ventricular; # myocardial infarction; ** left ventricular systolic dysfunction; †† cardiovascular; §§ glomerular filtration rate; |||| magnesium.

Study acronyms: AREA-IN-CHF = anti-remodelling effect of canrenone in patients with mild chronic heart failure; RALES = randomized aldactone evaluation study; EPHESUS = eplerenone post-acute myocardial infarction heart failure efficacy and survival study; EMPHASIS-HF = eplerenone in mild patients hospitalization and survival study in heart failure.
### Table 2. Definition of sudden cardiac death used in all the trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Sudden cardiac death definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akbulut et al</td>
<td>SCD data not reported.</td>
</tr>
<tr>
<td>AREA-IN-CHF</td>
<td>Any of witnessed instantaneous death in the absence of progressive circulatory failure lasting for 60 min or more; un-witnessed death in the absence of pre-existing progressive circulatory failure or other causes of death; death within 28 days after resuscitation from cardiac arrest in the absence of progressive pre-existing circulatory failure or other causes of death, death during attempted resuscitation; death within 60 min from the onset of new symptoms unless a cause other than cardiac was obvious.</td>
</tr>
<tr>
<td>Cicoira et al</td>
<td>Witnessed death from cardiac causes heralded by abrupt loss of consciousness within one hour after the onset of symptoms in a patient in whom death was unexpected.</td>
</tr>
<tr>
<td>RALES</td>
<td>Witnessed death from cardiac causes heralded by abrupt loss of consciousness within one hour after the onset of symptoms in a patient in whom death was unexpected.</td>
</tr>
<tr>
<td>EPHESUS</td>
<td>Death occurring within one hour of new symptoms, un-witnessed death with no new symptoms within the previous 72 hours, or cardiac arrest with death within 28 days thereafter.</td>
</tr>
<tr>
<td>EMPHASIS-HF</td>
<td>Witnessed death from cardiac causes heralded by abrupt loss of consciousness within one hour after the onset of symptoms in a patient in whom death was unexpected.</td>
</tr>
<tr>
<td>Skvortsov et al</td>
<td>SCD data reported but not defined.</td>
</tr>
<tr>
<td>Gao et al</td>
<td>SCD data not reported.</td>
</tr>
</tbody>
</table>
Table 3. Characteristics of MRAs usage, follow-up and number needed to treat to prevent SCD in all the trials

<table>
<thead>
<tr>
<th>Study</th>
<th>MRA used</th>
<th>Initial MRA dose, mg</th>
<th>Target MRA dose, mg</th>
<th>MRAs adherence, %</th>
<th>Mean follow-up, months</th>
<th>NNT* with MRAs to prevent one SCD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akbulut et al 28</td>
<td>Spironolactone</td>
<td>25</td>
<td>25</td>
<td>NR†</td>
<td>3</td>
<td>NR</td>
</tr>
<tr>
<td>AREA-IN-CHF 24</td>
<td>Canrenone</td>
<td>25</td>
<td>50</td>
<td>81</td>
<td>12</td>
<td>82</td>
</tr>
<tr>
<td>Cicoira et al 25</td>
<td>Spironolactone</td>
<td>25</td>
<td>12.5-50</td>
<td>87</td>
<td>12</td>
<td>51</td>
</tr>
<tr>
<td>RALES 11</td>
<td>Spironolactone</td>
<td>25</td>
<td>50</td>
<td>74</td>
<td>24</td>
<td>33</td>
</tr>
<tr>
<td>EPHESUS 26</td>
<td>Eplerenone</td>
<td>25</td>
<td>50</td>
<td>84</td>
<td>16</td>
<td>85</td>
</tr>
<tr>
<td>EMPHASIS-HF 12</td>
<td>Eplerenone</td>
<td>25</td>
<td>50</td>
<td>84</td>
<td>21</td>
<td>88</td>
</tr>
<tr>
<td>Skvortsov et al 27</td>
<td>Spironolactone</td>
<td>25</td>
<td>75</td>
<td>95</td>
<td>12</td>
<td>22</td>
</tr>
<tr>
<td>Gao et al 29</td>
<td>Spironolactone</td>
<td>20</td>
<td>20</td>
<td>NR</td>
<td>6</td>
<td>NR</td>
</tr>
</tbody>
</table>

\* number needed to treat; † not reported
Table 4. Characteristics of usage of evidence based interventions in all the trials

<table>
<thead>
<tr>
<th>Study</th>
<th>β-blocker use, MRA group (%)</th>
<th>β-blocker use, control group (%)</th>
<th>ACE-I* or ARB† use, MRA group (%)</th>
<th>ACE-I or ARB† use, control group (%)</th>
<th>ICD‡ use, MRA group (%)</th>
<th>ICD use, control group (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akbulut et al 26</td>
<td>0</td>
<td>50</td>
<td>NR§</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>AREA-IN-CHF 24</td>
<td>81.3</td>
<td>77.5</td>
<td>97</td>
<td>98.8</td>
<td>6.1</td>
<td>5.1</td>
</tr>
<tr>
<td>Cicoira et al 25</td>
<td>72</td>
<td>65</td>
<td>100</td>
<td>100</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>RALES 11</td>
<td>11</td>
<td>10</td>
<td>95</td>
<td>94</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>EPHESUS 26</td>
<td>75</td>
<td>75</td>
<td>86</td>
<td>87</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>EMPHASIS-HF 12</td>
<td>86.6</td>
<td>86.9</td>
<td>97.4</td>
<td>96.2</td>
<td>13</td>
<td>13.4</td>
</tr>
<tr>
<td>Skvortsov et al 27</td>
<td>63.1</td>
<td>53.3</td>
<td>100</td>
<td>100</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Gao et al 29</td>
<td>55</td>
<td>57</td>
<td>100</td>
<td>98</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

* angiotensin converting enzyme inhibitor; † angiotensin receptor blocker; ‡ implantable cardioverter–defibrillator; § not reported
Figure Legends

Figure 1. Flow diagram of study selection

Figure 2. Forest Plot comparing SCD, cardiovascular and total mortality in patients treated with and without MRAs
1894 articles identified
   678 MEDLINE
   1062 EMBASE
   10 Clinical trials databases
   143 Cochrane
   1 Other sources

285 duplicates removed

1609 potentially relevant articles identified for title and abstract review

1570 articles excluded as not relevant due to review articles, non-randomized design, registry data etc.

39 articles identified for full text review

31 articles excluded
   8 Enrolled patients without left ventricular systolic dysfunction
   7 Did not meet inclusion criteria
   7 Met inclusion criteria but did not report outcomes of interest or data unavailable
   6 Post-hoc analyses
   2 Ongoing trials
   1 Pilot study

8 trials included in the meta-analysis, of which-
   6 trials reported data on SCD and cardiovascular mortality, N=11654
   7 trials reported data on total mortality, N=11826
**Figure 2.**

<table>
<thead>
<tr>
<th></th>
<th>MRAs group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SCD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AREA-IN-CHF</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Cicoira et al.</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>RALES</td>
<td>82</td>
<td>110</td>
</tr>
<tr>
<td>EPHESUS</td>
<td>162</td>
<td>201</td>
</tr>
<tr>
<td>EMPHASIS-HF</td>
<td>60</td>
<td>76</td>
</tr>
<tr>
<td>Skvortsov et al.</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Summary</td>
<td>310</td>
<td>399</td>
</tr>
<tr>
<td><strong>CV Mortality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AREA-IN-CHF</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Cicoira et al.</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>RALES</td>
<td>226</td>
<td>314</td>
</tr>
<tr>
<td>EPHESUS</td>
<td>407</td>
<td>483</td>
</tr>
<tr>
<td>EMPHASIS-HF</td>
<td>147</td>
<td>185</td>
</tr>
<tr>
<td>Skvortsov et al.</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Summary</td>
<td>789</td>
<td>998</td>
</tr>
</tbody>
</table>

No. of events | Total No. of Patients | No. of events | Total No. of Patients | OR (95% CI)

- AREA-IN-CHF: 0.57 (0.16-1.99)
- RALES: 0.73 (0.54-0.99)
- EPHESUS: 0.79 (0.64-0.98)
- EMPHASIS-HF: 0.78 (0.55-1.11)
- Summary: 0.77 (0.66-0.89) p = 0.001

**Heterogeneity**

- Tau² = 0.00; Q = 0.67; p = 0.98; I² = 0.00
- Test for overall effect Z = 3.32; p = 0.001

**CV Mortality**

- AREA-IN-CHF: 0.63 (0.20-1.95)
- RALES: 0.63 (0.51-0.78)
- EPHESUS: 0.81 (0.71-0.94)
- EMPHASIS-HF: 0.77 (0.61-0.97)
- Skvortsov et al: 0.47 (0.08-2.61)
- Summary: 0.75 (0.68-0.84) p < 0.001

**Heterogeneity**

- Tau² = 0.00; Q = 4.36; p = 0.49; I² = 0.00
- Test for overall effect Z = 5.25; p < 0.001

Favors MRAs Favors Control
<table>
<thead>
<tr>
<th></th>
<th>MRAs group</th>
<th>Control group</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of events</td>
<td>Total No. of Patients</td>
<td>No. of events</td>
<td>Total No. of Patients</td>
</tr>
<tr>
<td>Akbulut et al.</td>
<td>0</td>
<td>35</td>
<td>0</td>
</tr>
<tr>
<td>Gao et al.</td>
<td>0</td>
<td>58</td>
<td>0</td>
</tr>
<tr>
<td>AREA-IN-CHF</td>
<td>6</td>
<td>231</td>
<td>12</td>
</tr>
<tr>
<td>Cicoira et al.</td>
<td>3</td>
<td>54</td>
<td>4</td>
</tr>
<tr>
<td>RALES</td>
<td>284</td>
<td>822</td>
<td>386</td>
</tr>
<tr>
<td>EPHESUS</td>
<td>478</td>
<td>3319</td>
<td>554</td>
</tr>
<tr>
<td>EMPHASIS-HF</td>
<td>171</td>
<td>1364</td>
<td>213</td>
</tr>
<tr>
<td>Summary</td>
<td>942</td>
<td>5883</td>
<td>1568</td>
</tr>
</tbody>
</table>

Heterogeneity

$\tau^2 = 0.01; \, Q = 6.74; \, p = 0.15; \, I^2 = 40.7$

Test for overall effect

$Z = 5.4; \, p < 0.001$

For expansion of study names see table 1.
The Effects of Mineralocorticoid Receptor Antagonists on the Risk of Sudden Cardiac Death in Patients with Left Ventricular Systolic Dysfunction: A Meta-analysis of Randomized Controlled Trials
Srinivas R. Bapoje, Amit Bahia, John E. Hokanson, Pamela N. Peterson, Paul A. Heidenreich, JoAnn Lindenfeld, Larry A. Allen and Frederick A. Masoudi

Circ Heart Fail. published online February 12, 2013; Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circheartfailure.ahajournals.org/content/early/2013/02/12/CIRCHEARTFAILURE.112.000003

Data Supplement (unedited) at:
http://circheartfailure.ahajournals.org/content/suppl/2013/02/12/CIRCHEARTFAILURE.112.000003.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Heart Failure can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Heart Failure is online at:
http://circheartfailure.ahajournals.org//subscriptions/
SUPPLEMENTAL MATERIAL

A. Search Methods:

Key words used for the search strategy - Aldosterone antagonists, block*, spironolactone, Aldactone®, eplerenone, Inspra®, canrenoate, canrenoic acid, canrenone, cardiovascular disease, cardiomyopathy, congestive heart failure, left ventricular systolic dysfunction, left ventricular systolic failure, left heart failure.

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

1 exp Aldosterone Antagonists/ or aldosterone antagonists.mp. (7221)
2 aldosterone block$.mp. (302)
3 exp Spironolactone/ or Spironolactone.mp. (6700)
4 aldactone.mp. (272)
5 eplerenone.mp. (762)
6 inspra.mp. (27)
7 canrenoic acid.mp. or exp Canrenoate Potassium/ (289)
8 canrenone.mp. or exp Canrenone/ (294)
9 (or/1-8) and (19$ or 200$ or 2010* or 2011$ or 201201$ or 201202$ or 201203$).ed. (8552)
10 cardiovascular disea$e.mp. or exp Cardiovascular Diseases/ (1741496)
11 cardiomyopathy.mp. or exp Cardiomyopathies/ (81253)
12 congestive heart failure.mp. or exp heart failure/ (90737)
13 systolic dysfunction.mp. or exp heart failure, systolic/ (4815)
14 exp ventricular dysfunction, left/ (18946)
15 left ventricular systolic failure.mp. (7)
16     left ventricular systolic dysfunction.mp. (1769)
17     left heart failure.mp. (632)
18     10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (1751507)
19     9 and 18 (3545)
20     limit 19 to "all child (0 to 18 years)" (204)
21     limit 19 to "all adult (19 plus years)" (1350)
22     20 not 21 (87)
23     19 not 22 (3458)
24     limit 23 to clinical trial, all (434)
26     clinical trial.pt. (470619)
27     random$.ti,ab. (600311)
28     double blind method/ (115253)
29     26 or 27 or 28 (925646)
30     23 and 29 (628)
31     24 or 30 (678)
**Supplemental Table 1.** Quality assessment of the studies included

<table>
<thead>
<tr>
<th>Author</th>
<th>Adequate sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding of participants, personnel and outcome assessors</th>
<th>Incomplete outcome data addressed</th>
<th>Free of Selective outcome reporting</th>
<th>Free of other bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akbulut et al</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>No</td>
</tr>
<tr>
<td>AREA-IN-CHF</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cicoira et al</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>RALES</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>EPHESUS</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>EMPHASIS-HF</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Skvortsov et al</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Gao et al</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Supplemental Figure 1. Funnel plot of Publication bias

Funnel Plot of Precision by Log odds ratio

Precision (1/Std Err) vs Log odds ratio