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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

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Abstract

Background—Sudden cardiac death (SCD) is an important cause of death in patients with left ventricular systolic dysfunction. 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 left ventricular systolic dysfunction.

Methods and Results—We systematically searched PubMed, EMBASE, Cochrane, and other databases through March 30, 2012, without language restrictions. We included trials that enrolled patients with left ventricular ejection fraction of $\geq 45\%$, randomized subjects to MRAs versus control and reported outcomes on SCD, total and cardiovascular mortality. Eight published trials that enrolled 11875 patients met inclusion criteria. Of these, 6 reported data on SCD and cardiovascular mortality, and 7 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 (odds ratio, 0.77; 95% confidence interval, 0.66–0.89; $P=0.001$). Similar reductions were observed in cardiovascular (0.75; 95% confidence interval, 0.68–0.84; $P<0.001$) and total mortality (odds ratio, 0.74; 95% confidence interval, 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 left ventricular systolic dysfunction. 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 therapy are needed to guide clinical decision-making.

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Disclosures

None.

Keywords

left ventricular systolic dysfunction; meta-analysis; mineralocorticoid receptor antagonists; sudden cardiac death

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 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.¹ Because the index of 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.^{2,3} ICD therapy is expensive, however, and many patients clinically eligible for primary prevention ICD therapy do not receive appropriate therapy.^{4,5} 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.^{6,7}

Abnormal neurohumoral signaling by the renin–angiotensin–aldosterone signaling contributes to the pathophysiologic basis of SCD in patients with LVSD.⁸ In animal models, suppression of the renin–angiotensin–aldosterone system by eplerenone attenuates heart failure–related ventricular electric remodeling and tachyarrhythmia vulnerability.⁹ Some clinical trials evaluating the blockade of renin–angiotensin–aldosterone in patients with LVSD have shown reductions in mortality from SCD^{10,11}; however, other studies have failed to reproduce these results.¹² 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,¹³ the limited effectiveness of and side effects profiles of antiarrhythmic drugs,¹⁴ and the incomplete neurohumoral suppression by angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB).¹⁵ Although meta-analyses have explored the effect of ACEI on SCD,¹⁶ similar analyses assessing 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 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 language restrictions through March 30, 2012, for randomized controlled trials, using the key words of “aldosterone antagonists, spironolactone, Aldactone, eplerenone, Inspira, canrenone, canrenoate, heart failure, systolic failure, systolic dysfunction, congestive heart failure, and cardiovascular disease” (see online-only Data Supplement for full search strategy). We also searched abstracts of major US cardiovascular medicine conference proceedings (American Heart Association [AHA] and American College of Cardiology), 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 enrolled adult patients with symptomatic or asymptomatic heart failure with LVSD (defined as left ventricular ejection fraction (EF) of $\leq 45\%$); assigned patients to MRA therapy versus placebo or control; reported data on SCD, or total and cardiovascular (CV) mortality; had a study duration and a follow-up of ≥ 2 months; and 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 3 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 American College of Cardiology/AHA/European Society of Cardiology 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 (S.R.B. and A.B.) screened the abstracts of all the citations obtained by the initial search in a standardized and unblinded 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 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, and details of intervention and number 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 to prevent 1 SCD for each study. The studies that met our inclusion criteria were evaluated for the risk of bias using a 6-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 2 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% confidence interval (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 because we anticipated heterogeneity between the trials.²⁰ Clinical heterogeneity between the trials was explored by using subgroup analysis by random effects model based on definition of SCD (AHA/ European Society of Cardiology guidelines versus other definition), MRA agent used (eplerenone versus spironolactone and canrenone), and the degree of LVSD (EF $\leq 35\%$ versus $\leq 45\%$). Because canrenone is an active metabolite of spironolactone, we combined trials using spironolactone and canrenone for the MRA subgroup analysis.²¹ 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, antiarrhythmic agents and ICDs as covariates.²² 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 because of 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.²³ A priori, we defined significant heterogeneity between trials as an I^2 value of $>50\%$. We assessed for evidence of publication bias by constructing a funnel plot and Eggers test. A 2-sided P value of <0.05 was considered statistically significant for all analysis. Statistical analysis was performed using Comprehensive Metaanalysis Version 2 (Biostat, Englewood NJ).

Results

Our initial search strategy yielded 1887 studies (Figure 1, Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram). Of these, 8 randomized controlled trials enrolling a total of 11 875 patients met our inclusion criteria.^{11, 12,24–29} The study characteristics of all the trials are summarized in Tables 1–4. Six trials enrolling 11654 patients reported data on SCD and CV mortality,^{11, 12,25–27} and 7 trials enrolling 11826 patients reported data on total mortality.^{11,12,24–26,28,29} TWO trials met criteria for poor methodological quality,^{27,28} and the other 6 trials met criteria for good quality (Table I in the online-only Data Supplement for quality assessment data for the trials). The Eplerenone Postacute Myocardial Infarction Heart Failure Efficacy and Survival Study (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 nonischemic 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, whereas Randomized Aldactone Evaluation Study 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 American College of Cardiology/AHA/ European Society of Cardiology guidelines (Table 2).¹⁸ Adherence with MRAs in the intervention groups when measured varied from 74% to 95%. All the trials reported $>80\%$ usage of ACEI 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.

SCD, CV Mortality, and Total Mortality

There were a total of 709 SCDs among 11654 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 in order to prevent 1 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 with 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 recomputing the summary OR found similar point estimates. In particular, the results were unchanged when EPHEBUS, 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 2-tailed P value of 0.01 for SCD and a visually asymmetrical funnel plot (Figure I in the online-only Data Supplement). We calculated that the number of missing studies needed to raise the P value for significance >0.05 to be 9. 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).

Subgroup Analysis for SCD

The overall result did not change substantially when we limited the study to trials using the 2006 American College of Cardiology/AHA/European Society of Cardiology practice guidelines on definition of SCD^{11,12,25} that enrolled 4506 patients, compared with trials using other definitions that enrolled 7148 patients,^{24,26,27} with OR 0.75 (95% CI, 0.60–0.94; $P=0.01$) versus 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 with OR, 0.78 (95% CI, 0.63–0.96; $P=0.02$) for trials that enrolled 7205 patients with an EF of $>45\%$.^{24–26} 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 antiarrhythmic drugs, statins, and ICD, was reported inconsistently. All trials reported $>80\%$ 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 metaregression modeling of the log-odds of SCD against β -blocker usage of $\geq 75\%$ or $<75\%$. There was no significant change in the odds of SCD between trials that reported $\geq 75\%$ baseline usage of β -blockers compared with 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 receiving spironolactone or eplerenone, and across studies that used standard and nonstandard definitions of SCD. A meta-regression modeled on β -blocker usage did not show any difference in mortality benefit among trials with $>75\%$ or $<75\%$ usage of β -blockers.

The substantial reduction in the risk of SCD with MRA 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 underused class of medications in patients with heart failure³⁰ and have a high potential impact on reduction of

mortality among evidence-based therapies for heart failure with optimal implementation.³¹ Third, the benefits of eplerenone on SCD 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.^{32,33} Finally, we found a similar effect in the subgroup of patients with milder LVSD (45% versus 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 renin–angiotensin–aldosterone system, MRAs potentiate the effect of ACEI and ARBs on ventricular remodeling in HF and post-MI patients.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.^{35–37} The reduced electric 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.^{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.⁴⁰ Finally, the MRAs prevent elevated Cortisol from activating mineralocorticoid receptors resulting in decreased substrate for arrhythmias and SCD.⁴¹

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 Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) trial that randomized patients with LVSD with EF of 35% in New York Heart Association 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.³ None of the patients received MRA therapy, however. The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure trial, which randomized 1520 patients with left ventricular EF 35% in New York Heart Association class III or IV heart failure on optimal medical therapy to no cardiac resynchronization therapy and cardiac resynchronization therapy with and without defibrillator, found a 20% risk reduction in cardiovascular death in both cardiac resynchronization therapy with and without defibrillator arms.⁴² 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, because the medical therapy in the trials of ICDs was optimized from MADIT I (Multicenter Automatic Defibrillator Implantation Trial I) to SCD-HeFT, the degree of superiority of the ICD compared with 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 nonischemic 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.¹³ 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 the same regardless of the definition of SCD runs counter to the concern that the use of nonstandard 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 nonstandard definition of SCD. Because we did not identify differences in SCD rates on subgroup analysis, we infer that the use of nonstandard definitions did not have a significant effect on our conclusions. Third, we identified publication bias in 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 prespecified inclusion criteria to prevent publication bias as we did in this study. Although this bias could have influenced our results, we think it is highly unlikely that we failed to identify the number of randomized controlled trials 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 SEM. 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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CLINICAL PERSPECTIVE

Sudden cardiac death is an important cause of mortality in patients with heart failure and left ventricular systolic dysfunction. Mineralocorticoid receptor antagonists, like spironolactone and eplerenone, have the potential to mitigate this risk of sudden death because of their effect on renin–angiotensin–aldosterone pathway. We examined this effect of mineralocorticoid receptor antagonists on sudden cardiac death by performing a meta-analysis of randomized clinical trials of aldosterone antagonists for patients with left ventricular systolic dysfunction. In this pooled analysis, aldosterone antagonists were associated with a 23% risk reduction of sudden cardiac death. Thus, although they are widely recommended in guidelines for eligible patients with left ventricular systolic dysfunction, aldosterone antagonists may be particularly important in patients who decline or are otherwise ineligible for implantable cardioverter defibrillator therapy. Comparative effectiveness studies of these drugs on sudden cardiac death in the usual care setting as well as a prospective clinical trial evaluating the efficacy of implantable cardioverter defibrillator therapy to prevent sudden cardiac death in patients receiving optimal medical therapy are needed to guide clinical decision-making.

Figure 1.

Flow diagram of study selection. SCD indicates sudden cardiac death.

Figure 2.

Forest Plot comparing sudden cardiac death (SCD), cardiovascular, and total mortality in patients treated with and without mineralocorticoid receptor antagonists (MRAs). AREA-IN-CHF indicates Antiremodeling Effect of Canrenone in Patients with Mild Chronic Heart failure; CI, confidence interval; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; EPHESUS, Eplerenone Postacute Myocardial Infarction Heart Failure Efficacy and Survival Study; OR, odds ratio; and RALES, Randomized Aldactone Evaluation Study.

Table 1

Baseline Characteristics of All Trials

Study, Year	MRAs Treatment Group	MRAs Control Group	Inclusion EF, %	Inclusion Creatinine, $\mu\text{mol/L}$	Study Subjects	NYHA Class	Primary Outcome, Effect of MRAs on	Mean EF in MRAs Group, % $\pm$ SD	Mean EF in Control Group, % $\pm$ SD	Study Center Type
Akbulut et al., ²⁸ 2003	35	70	35	176.8	Chronic CHF	3	QT dispersion	27.2 $\pm$ 2	27.7 $\pm$ 3	Single
AREA-IN-CHF, ²⁴ 2009	231	236	45	221	Chronic CHF	2	LV remodeling and function	39.9 $\pm$ 8.6	39.7 $\pm$ 8.6	Multi
Cicoira et al., ²⁵ 2002	54	52	45	150.2	Chronic CHF	1–3	LV function and exercise tolerance	33 $\pm$ 7	34 $\pm$ 7	Single
RALES, ¹¹ 1999	822	841	35	221	Chronic CHF	2–4	Total mortality	25.6 $\pm$ 6.7	25.2 $\pm$ 6.8	Multi
EPHESUS, ²⁶ 2003	3319	3313	40	221	Post-MI with LVSD	NR	Total and CV mortality, hospitalization for CV causes	33 $\pm$ 6	33 $\pm$ 6	Multi
EMPHASIS-HF, ¹² 2011	1364	1373	35	GFR <30 mL/min	Chronic CHF	2	Composite of death and hospitalization for CHF	26.2 $\pm$ 4.6	26.1 $\pm$ 4.7	Multi
Skvortsovetal, ²⁷ 2007	19	30	35	150.2	Chronic CHF	2–4	LV remodeling, safety and clinico-funct. status	27.3 $\pm$ 7.5	31.2 $\pm$ 3.5	Single
Gao et al., ²⁹ 2007	58	58	<45	221	Chronic CHF	2–4	Mg level and arrhythmias	42 $\pm$ 11	43 $\pm$ 10	Single

AREA-IN-CHF indicates Antiremodeling Effect of Canrenone in Patients with Mild Chronic Heart failure; CHF, congestive heart failure; CV, cardiovascular; EF, ejection fraction; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; EPHESUS, Eplerenone Postacute Myocardial Infarction Heart Failure Efficacy and Survival Study; GFR, glomerular filtration rate; LV, left ventricular; LVSD, left ventricular systolic dysfunction; Mg, magnesium; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; and RALES, Randomized Aldactone Evaluation Study.

Table 2**Definition of Sudden Cardiac Death Used in All the Trials**

Study	Sudden Cardiac Death Definition
Akbulut et al ²⁸	Sudden cardiac death data not reported
AREA-IN-CHF ²⁴	Any of witnessed instantaneous death in the absence of progressive circulatory failure lasting for 60 min; unwitnessed 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
Cicoira et al ²⁵	Witnessed death from cardiac causes heralded by abrupt loss of consciousness within 1 hour after the onset of symptoms in a patient in whom death was unexpected
RALES ¹¹	Witnessed death from cardiac causes heralded by abrupt loss of consciousness within 1 hour after the onset of symptoms in a patient in whom death was unexpected
EPHESUS ²⁶	Death occurring within 1 hour of new symptoms, unwitnessed death with no new symptoms within the previous 72 hours, or cardiac arrest with death within 28 days thereafter
EMPHASIS-HF ¹²	Witnessed death from cardiac causes heralded by abrupt loss of consciousness within 1 hour after the onset of symptoms in a patient in whom death was unexpected
Skvortsov et al ²⁷	Sudden cardiac death data reported but not defined
Gao et al ²⁹	Sudden cardiac death data not reported

AREA-IN-CHF indicates Antiremodeling Effect of Canrenone in Patients with Mild Chronic Heart failure; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; EPHESUS, Eplerenone Postacute Myocardial Infarction Heart Failure Efficacy and Survival Study; and RALES, Randomized Aldactone Evaluation Study.

Table 3
Characteristics of MRAs Usage, Follow-Up, and Number Needed to Treat to Prevent SCD in All the Trials

Study	MRA Used	Initial MRA Dose, mg	Target MRA Dose, mg	MRAs Adherence, %	Mean Follow-Up, mo	NNT With MRAs to Prevent 1 SCD
Akbulut et al ²⁸	Spirolonolactone	25	25	NR	3	NR
AREA-IN-CHF ²⁴	Canrenone	25	50	81	12	82
Cicoira et al ²⁵	Spirolonolactone	25	12.5-50	87	12	51
RALES ¹¹	Spirolonolactone	25	50	74	24	33
EPHESUS ²⁶	Eplerenone	25	50	84	16	85
EMPHASIS-HF ¹²	Eplerenone	25	50	84	21	88
Skvortsov et al ²⁷	Spirolonolactone	25	75	95	12	22
Gao et al ²⁹	Spirolonolactone	20	20	NR	6	NR

AREA-IN-CHF indicates Antiremodeling Effect of Canrenone in Patients with Mild Chronic Heart failure; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; EPHESUS, Eplerenone Postacute Myocardial Infarction Heart Failure Efficacy and Survival Study; MRA, mineralocorticoid receptor antagonists; NNT, number needed to treat; NR, not reported; RALES, Randomized Aldactone Evaluation Study; and SCD, sudden cardiac death.

Table 4

Characteristics of Usage of Evidence-Based Interventions in All the Trials

Study	β -Blocker Use, MRA Group, %	β -Blocker Use, Control Group, %	ACEI or ARB Use, MRA Group, %	ACEI or ARB Use, Control Group, %	ACEI or ARB Use, MRA Group, %	ACEI or ARB Use, Control Group, %	ICD Use, MRA Group, %	ICD Use Control Group, %
Akbulut et al ²⁸	0	50	NR	NR	NR	NR	NR	NR
AREA-IN-CHF ²⁴	81.3	77.5	97	97	98.8	98.8	6.1	5.1
Cicoira et al ²⁵	72	65	100	100	100	100	1	1
RALES ¹¹	11	10	95	95	94	94	NR	NR
EPHESUS ²⁶	75	75	86	86	87	87	NR	NR
EMPHASIS-HF ¹²	86.6	86.9	97.4	97.4	96.2	96.2	13	13.4
Skvortsov et al ²⁷	63.1	53.3	100	100	100	100	NR	NR
Gao et al ²⁹	55	57	100	100	98	98	2	3

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ICD, implantable cardioverter defibrillator; MRA, mineralocorticoid receptor antagonists; and NR, not reported.