ORIGINAL ARTICLE

Routine Spironolactone in Acute Myocardial Infarction

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ABSTRACT

BACKGROUND

Mineralocorticoid receptor antagonists have been shown to reduce mortality in patients after myocardial infarction with congestive heart failure. Whether routine use of spironolactone is beneficial after myocardial infarction is uncertain.

METHODS

In this multicenter trial with a 2-by-2 factorial design, we randomly assigned patients with myocardial infarction who had undergone percutaneous coronary intervention to receive either spironolactone or placebo and either colchicine or placebo. The results of the spironolactone trial are reported here. The two primary outcomes were a composite of death from cardiovascular causes or new or worsening heart failure, evaluated as the total number of events; and a composite of the first occurrence of myocardial infarction, stroke, new or worsening heart failure, or death from cardiovascular causes. Safety was also assessed.

RESULTS

We enrolled 7062 patients at 104 centers in 14 countries; 3537 patients were assigned to receive spironolactone and 3525 to receive placebo. At the time of our analyses, the vital status was unknown for 45 patients (0.6%). For the first primary outcome, there were 183 events (1.7 per 100 patient-years) in the spironolactone group as compared with 220 events (2.1 per 100 patient-years) in the placebo group over a median follow-up period of 3 years (hazard ratio adjusted for competing risk of death from noncardiovascular causes, 0.91; 95% confidence interval [CI], 0.69 to 1.21; P=0.51). With respect to the second primary outcome, an event occurred in 280 of 3537 patients (7.9%) in the spironolactone group and 294 of 3525 patients (8.3%) in the placebo group (hazard ratio adjusted for competing risk, 0.96; 95% CI, 0.81 to 1.13; P=0.60). Serious adverse events were reported in 255 patients (7.2%) in the spironolactone group and 241 (6.8%) in the placebo group.

CONCLUSIONS

Among patients with myocardial infarction, spironolactone did not reduce the incidence of death from cardiovascular causes or new or worsening heart failure or the incidence of a composite of death from cardiovascular causes, myocardial infarction, stroke, or new or worsening heart failure. (Funded by the Canadian Institutes of Health Research and others; CLEAR ClinicalTrials.gov number, NCT03048825.)

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*A complete list of the CLEAR investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on November 17, 2024, at NEJM.org.

DOI: 10.1056/NEJMoa2405923

Inhibition of the renin–angiotensin–aldosterone system with an angiotensin-converting–enzyme inhibitor improves outcomes in patients after myocardial infarction.[1,2] Higher aldosterone levels have been associated with increased mortality after myocardial infarction.[3] Aldosterone antagonism with spironolactone has been shown to reduce mortality among patients with chronic heart failure with reduced ejection fraction, and is a cornerstone of therapy.[4] Aldosterone antagonism also reduces heart failure in patients with preserved ejection fraction and heart failure.[5]

Aldosterone antagonism with eplerenone has been shown to improve outcomes in patients with acute myocardial infarction who have heart failure with reduced ejection fraction, but whether aldosterone antagonism is beneficial in all patients after myocardial infarction remains uncertain.[6] Recent attempts to improve outcomes with intensified renin–angiotensin–aldosterone inhibition have not shown improvements in outcomes.[7,8] A trial of routine aldosterone antagonism with spironolactone in addition to standard therapy among 1603 patients after myocardial infarction without heart failure showed no improvement in outcomes.[9] However, there was a significant reduction in mortality in the subgroup of 1229 patients with ST-segment elevation myocardial infarction (STEMI), a finding that highlights the need for a large trial. Finally, an additional randomized trial involving patients with STEMI without heart failure showed that eplerenone reduced B-type natriuretic peptide levels.[10] We conducted the CLEAR trial to evaluate whether routine use of spironolactone is beneficial in patients after myocardial infarction.

Methods

Trial Design

We used a 2-by-2 factorial design in this international, investigator-initiated, prospective, randomized, placebo-controlled trial of spironolactone as compared with placebo and colchicine as compared with placebo in patients with acute myocardial infarction. Details of the trial design have been published previously[11] and are provided in the protocol, available with the full text of this article at NEJM.org. Here we report the results of the trial of spironolactone as compared with placebo; the results of the trial of colchicine as compared with placebo are reported separately.[12] All patients, investigators, health care providers, data collectors, and outcome adjudicators were unaware of trial-group assignments. A registry-based trial of SYNERGY stents in 733 patients with STEMI was embedded within the larger trial of colchicine and spironolactone, and the results of the registry-based trial have been published previously.[13]

Initially, patients were eligible for the trial only if they had STEMI and had undergone percutaneous coronary intervention. To increase recruitment, the steering committee modified the protocol on April 5, 2020, to enroll patients with large non–ST-segment elevation myocardial infarction (NSTEMI) who had undergone percutaneous coronary intervention and had one or more of the following risk factors: a left ventricular ejection fraction of no more than 45%; diabetes mellitus; multivessel coronary artery disease, defined by at least 50% stenosis of a second major epicardial vessel; previous myocardial infarction; or age greater than 60 years. The detailed eligibility criteria are provided in Table S1 in the Supplementary Appendix, available at NEJM.org.

The ethics committee at each participating center and the relevant national regulatory authorities approved the trial. All patients provided written informed consent. The Population Health Research Institute at McMaster University and Hamilton Health Sciences in Hamilton, Canada, coordinated the trial, collected and held all trial data, and conducted all analyses. The steering committee designed the trial protocol, and the members of the committee (listed in the Supplementary Appendix) vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The trial funders had no role in the design and conduct of the trial. An independent data and safety monitoring committee monitored the accumulating safety and efficacy data.

Randomization

Patients were randomly assigned in a factorial 1:1:1:1 allocation to receive spironolactone and colchicine, colchicine and placebo, spironolactone and placebo, or placebo only as soon as possible after the index percutaneous coronary intervention. Randomization was performed with the use of permuted blocks within a 24-hour computerized central system at the Population Health Research Institute. Randomization was stratified

according to trial center and the type of myocardial infarction (STEMI or NSTEMI).

OUTCOMES

The primary efficacy outcomes were a composite of death from cardiovascular causes or new or worsening heart failure, evaluated as the total number of events; and a composite of the first occurrence of myocardial infarction, stroke, new or worsening heart failure, or death from cardiovascular causes, evaluated in a time-to-event analysis. The total number of events reflects the totality of an intervention because it includes recurrent events. Key secondary outcomes were a composite of the first occurrence of new or worsening heart failure, clinically significant ventricular arrhythmia, or death from cardiovascular causes; death from cardiovascular causes; and a composite of the first occurrence of new or worsening heart failure or death from cardiovascular causes; each of these secondary outcomes was evaluated in a time-to-event analysis. Blood pressure and safety were also assessed. Safety outcomes included hyperkalemia (serum potassium >5.5 mmol per liter); a composite of death from renal causes, dialysis, renal transplantation, or a sustained drop in the estimated glomerular filtration rate (eGFR) of at least 40%; and components of the composite outcome.

A committee of clinicians who were unaware of trial-group assignments adjudicated all primary-outcome events, episodes of major bleeding, and episodes of stent thrombosis. Staff at an angiographic core laboratory at the Population Health Research Institute who were unaware of trial-group assignments reviewed all ischemia-driven revascularization and stent thrombosis events. Detailed definitions of outcomes are provided in Table S2.

TRIAL INTERVENTIONS

The trial products were spironolactone tablets of 25 mg, colchicine tablets of 0.5 mg, and placebos matching the colchicine and spironolactone tablets. Tiofarma provided both trial drugs and placebos, which were manufactured with raw materials produced by Indena.

STATISTICAL ANALYSIS

The initial calculation of sample size to provide the trial with 80% power to detect a 25% relative risk reduction was based on a time-to-event analysis of death from cardiovascular causes or new or worsening heart failure; we anticipated a cumulative incidence of events in the placebo group of 15% at 3 years, a two-sided type I error level of 5%, a loss to follow-up of 2% of patients in both the spironolactone group and the placebo group, discontinuation of the trial regimen by 12.5% of patients, and no interaction with colchicine. On the basis of these assumptions, we estimated that 4000 patients and 512 primary-outcome events were needed to detect a 25% relative risk reduction with a log-rank test. In April 2020, the fourth author performed a blinded interim analysis of the incidence of events and found an incidence of 3% per patient-year, with an estimated cumulative incidence of 9% at 3 years, which was consistent with the data from several recent trials.[14] As a result, the sample size was increased from 4000 to 7000 patients to maintain a power of 80%, and we estimated that 546 primary-outcome events would be sufficient to detect a 25% relative risk reduction. The sample size was increased without knowledge of any treatment effects.

In October 2023, blinded analysis showed an overall incidence of first events of death from cardiovascular causes or new or worsening heart failure of 4%. Given the lower-than-expected incidence of events, in December 2023, we decided to proceed with two primary outcomes but preserve the type I error rate at 5%. The type I error rate was partitioned to 4% for the first primary outcome (death from cardiovascular causes or new or worsening heart failure) and 1.85% for the second primary outcome (a composite of the first occurrence of myocardial infarction, stroke, new or worsening heart failure, or death from cardiovascular causes), because the overall blinded data indicated an overlap of 57% of events between the two primary outcomes. We estimate that a sample size of 7000 patients would provide the trial with 84% power to detect a relative risk reduction of 31.5% with the use of the Prentice–Williams–Peterson model for the first primary outcome, with an incidence of events in the placebo group of 6% (357 events) over 3 years. Furthermore, we estimated that this sample size would provide the trial with 80% power to detect a 26% relative risk reduction with the use of a log-rank test for the second primary outcome, with an incidence of events in the placebo group of 10.5% (644 events) over 3 years.

The prespecified primary analysis was performed according to the intention-to-treat principle. The first primary outcome (death from cardiovascular causes or new or worsening heart failure) was analyzed as the total number of events with the use of the Prentice–Williams–Peterson conditional gap-time model. The second primary outcome (a composite of death from cardiovascular causes, recurrent myocardial infarction, stroke, or new or worsening heart failure) was assessed in a time-to-first-event analysis with the log-rank test for the P value; for the effect size and 95% confidence intervals, we used a Cox proportional-hazards model with patients stratified according to whether they received colchicine or colchicine-matched placebo and whether they had STEMI or NSTEMI. In a post hoc analysis requested by the *Journal*, we used the method of Ghosh and Lin for the total number of events and the Fine–Gray subdistribution hazard model for the time-to-first-event analysis to account for competing risks of death from noncardiovascular causes (in outcomes that include death from cardiovascular causes), death from cardiovascular causes (in outcomes that include death from noncardiovascular causes), and death from any cause (in other, nonfatal outcomes). Secondary outcomes were analyzed with the same approach. The widths of the confidence intervals have not been adjusted for multiplicity, and the intervals may not be used in place of hypothesis testing. An interaction among the assigned trial regimens was not expected but was tested at a level of significance of 5%. The safety outcomes were assessed in the on-treatment analysis.

The data and safety monitoring committee reviewed unblinded data for efficacy in two interim analyses, on October 12, 2021, and October 17, 2022 (further details are provided in the Supplementary Appendix). In addition, systolic blood pressure, diastolic blood pressure, and eGFR were analyzed with a linear mixed model with repeated measures and adjusted according to the baseline values; the least-squares mean with standard error and the mean difference with 95% confidence interval are reported.

The prespecified subgroups were analyzed with the use of the Cox regression model with an interaction term for the subgroup. Patients were divided into subgroups according to the prespecified characteristics: age (≥65 vs. <65 years), sex (female vs. male), type of myocardial infarction (anterior STEMI vs. other myocardial infarction), serum potassium concentration at baseline (<4 mmol per liter vs. ≥4 mmol per liter), history of hypertension versus no history of hypertension, and timing of enrollment with respect to the coronavirus disease 2019 (Covid-19) pandemic (before [February 1, 2018, through January 30, 2020], during [January 31, 2020, through January 31, 2022], or after [February 1, 2022, to the time of analysis] the pandemic). We hypothesized that the effects of the trial regimen would be consistent across the subgroups stratified according to age and sex; that the benefits would be greater in the subgroups with anterior STEMI, a serum potassium concentration at baseline of less than 4 mmol per liter, and a history of hypertension than in the counterpart subgroups; and that the effects would be reduced in the subgroup enrolled during the Covid-19 pandemic as compared with the subgroups enrolled before or after the pandemic. Geographic region (North America vs. Europe vs. other) was added as a post hoc subgroup to demonstrate consistency. We did not collect information about left ventricular ejection fraction, and we are unable to report results from subgroups stratified according to this characteristic. We undertook a prespecified on-treatment analysis that excluded patients who discontinued the trial regimen on the day of randomization and censored patients 7 days after permanent discontinuation of the trial regimen.

RESULTS

PATIENTS

Between February 1, 2018, and November 8, 2022, we enrolled 7062 patients from 104 centers in 14 countries; 3537 were assigned to receive spironolactone and 3525 to receive placebo (Fig. S1). At the time of our analyses, the vital status was unknown for 45 of the 7062 patients (0.6%). Given that the missing data were rare and evenly distributed between the spironolactone and placebo groups, the data are most likely missing at random. Baseline characteristics of the patients appeared to be well balanced between the groups; the mean age of patients was 61 years, and 20.4% of patients were women (Table 1). A total of 9.0% of patients had previous myocardial infarction, 0.8% had a history of heart failure, and 18.5% had diabetes mellitus. Most patients who underwent randomization had STEMI (95.1%), and 4.9% had NSTEMI.

Table 1. Demographic and Clinical Characteristics at Baseline.*

Characteristic	Spironolactone (N=3537)	Placebo (N=3525)
Demographic characteristics		
Mean age — yr	60.9±10.3	60.4±10.3
Age >75 yr — no. (%)	294 (8.3)	277 (7.9)
Female sex — no. (%)	760 (21.5)	678 (19.2)
Geographic region		
North America	1009 (28.5)	1013 (28.7)
Europe	2366 (66.9)	2349 (66.6)
Other	162 (4.6)	163 (4.6)
Clinical characteristics		
Killip class ≥II — no. (%)†	24 (0.7)	25 (0.7)
NSTEMI at presentation — no. (%)	168 (4.7)	181 (5.1)
STEMI at presentation — no. (%)	3369 (95.3)	3344 (94.9)
Myocardial area affected by STEMI — no./total no. (%)		
Anterior	1315/3369 (39.0)	1315/3344 (39.3)
Inferior	1942/3369 (57.6)	1890/3344 (56.5)
Lateral	434/3369 (12.9)	423/3344 (12.6)
Posterior	328/3369 (9.7)	332/3344 (9.9)
Multivessel coronary disease — no. (%)	1725 (48.8)	1752 (49.7)
Medical history — no. (%)		
Previous heart failure	24 (0.7)	35 (1.0)
Current smoker	1440 (40.7)	1444 (41.0)
Hypertension	1600 (45.2)	1633 (46.3)
Diabetes mellitus	630 (17.8)	673 (19.1)
Previous myocardial infarction	321 (9.1)	312 (8.9)
Previous percutaneous coronary intervention	356 (10.1)	353 (10.0)
Medications at discharge — no. (%)		
Aspirin	3417 (96.6)	3416 (96.9)
Clopidogrel	1499 (42.4)	1476 (41.9)
Ticagrelor	1596 (45.1)	1586 (45.0)
Prasugrel	393 (11.1)	401 (11.4)
Angiotensin-converting–enzyme inhibitor or angiotensin-receptor blocker	2745 (77.6)	2773 (78.7)
Statin	3408 (96.4)	3416 (96.9)
Sodium–glucose cotransporter 2 inhibitor	113 (3.2)	98 (2.8)
Initial percutaneous coronary intervention‡		
Placement of bare-metal stent — no. of stents/total no. (%)	11/4854 (0.2)	9/4841 (0.2)
Placement of ≥1 drug-eluting stent — no. of stents/total no. (%)	4667/4854 (96.1)	4646/4841 (96.0)
Angioplasty only — no. of stents/total no. (%)	149/4854 (3.1)	162/4841 (3.3)
Placement of intraaortic balloon pump — no. of patients (%)	46 (1.3)	48 (1.4)

* Plus–minus values are means ±SD. NSTEMI denotes non–ST-segment elevation myocardial infarction, and STEMI ST-segment elevation myocardial infarction.
† The Killip classification system is a tool to assess the risk of death based on the severity of heart failure in patients with acute myocardial infarction. The scale ranges from I to IV, with higher numbers indicating greater risk.
‡ The total number of stents placed was 9695, with 4854 in the spironolactone group and 4841 in the placebo group.

The median time from the onset of myocardial infarction to randomization was 26.8 hours (interquartile range, 15.9 to 42.4), and the median time from randomization to the first dose of the trial product was 2.1 hours (interquartile range, 0.7 to 9.2). The medications provided to patients at discharge from the hospital appeared to be similar in the two groups (Table 1).

The median duration of follow-up was 3.00 years (interquartile range, 2.14 to 3.71); 28.0% of patients in the spironolactone group and 24.4% in the placebo group discontinued the trial regimen. In the case of 140 patients (4.0%) in the spironolactone group and 166 (4.7%) in the placebo group, the treating physician prescribed open-label spironolactone instead of the trial product.

BLOOD PRESSURE

The least-squares mean (±SE) systolic blood pressure at 1 year of follow-up, adjusted according to the baseline value, was 126.9±0.3 in 2724 patients in the spironolactone group and 129.7±0.3 in 2672 patients in the placebo group, with a mean difference of −2.8 (95% confidence interval [CI], −3.6 to −2.0). The least-squares mean diastolic blood pressure at 1 year of follow-up, adjusted according to the baseline value, was 77.5±0.2 in 2717 patients in the spironolactone group and 78.9±0.2 in 2660 patients in the placebo group, with a mean difference of −1.3 (95% CI, −1.8 to −0.8). A similar trend was observed at all time points.

EFFICACY

For the first primary outcome, there were 183 events (1.7 per 100 patient-years) in the spironolactone group as compared with 220 events (2.1 per 100 patient-years) in the placebo group (hazard ratio, 0.89; 95% CI, 0.73 to 1.08; P=0.23; hazard ratio adjusted for competing risk of death from noncardiovascular causes, 0.91; 95% CI, 0.69 to 1.21; P=0.51) (Table 2, Fig. 1A, and Table S3). With respect to the second primary outcome, an event occurred in 280 of 3537 patients (7.9%) in the spironolactone group as compared with 294 of 3525 (8.3%) in the placebo group (hazard ratio, 0.95; 95% CI, 0.80 to 1.12; P=0.52; hazard ratio adjusted for competing risk, 0.96; 95% CI, 0.81 to 1.13; P=0.60) (Table 2 and Fig. 1B). The colchicine factorial had no significant effect on the primary outcomes in the trial of spironolactone versus placebo (P=0.23 and 0.80 for interactions with first and second primary outcomes).

Cardiovascular mortality was similar in the two groups (3.2% in the spironolactone group vs. 3.3% in the placebo group [hazard ratio, 0.98; 95% CI, 0.76 to 1.27; hazard ratio adjusted for competing risk, 0.98; 95% CI, 0.76 to 1.27]) (Table 2). New or worsening heart failure occurred in 58 patients (1.6%) in the spironolactone group as compared with 84 (2.4%) in the placebo group (hazard ratio, 0.69; 95% CI, 0.49 to 0.96; hazard ratio adjusted for competing risk, 0.77; 95% CI, 0.51 to 1.16).

The baseline characteristics of the on-treatment population appeared to be well balanced between the two groups (Table S4). The on-treatment analyses included 131 events (1.5 per 100 patient-years) in the spironolactone group versus 179 events (2.0 per 100 patient-years) in the placebo group for the first primary outcome (hazard ratio, 0.79; 95% CI, 0.63 to 1.00), and the second primary outcome occurred in 204 patients (5.8%) in the spironolactone group versus 250 (7.2%) in the placebo group (hazard ratio, 0.83; 95% CI, 0.69 to 1.00) (Table S5). The incidence of the primary outcomes appeared to be consistent across all prespecified subgroups (Figs. S2 and S3).

SAFETY

Hyperkalemia (serum potassium >5.5 mmol per liter) leading to discontinuation of the trial regimen occurred in 39 patients (1.1%) in the spironolactone group and 20 (0.6%) in the placebo group (Table 3). Death from renal causes, dialysis, renal transplantation, or a sustained drop of at least 40% in the eGFR occurred in 37 patients (1.0%) in the spironolactone group and 44 (1.2%) in the placebo group (odds ratio, 0.84; 95% CI, 0.54 to 1.30) (Table 2). A sustained drop of at least 40% in the eGFR occurred in 32 patients (0.9%) in the spironolactone group and 38 (1.1%) in the placebo group (odds ratio, 0.84; 95% CI, 0.52 to 1.34) (Table 2). The least-squares mean (±SE) eGFR at 1 year of follow-up, adjusted according to the baseline value, was 88.5±0.3 ml per minute per 1.73 m^2 of body-surface area among 3537 patients in the spironolactone group and 90.2±0.3 ml per minute per 1.73 m^2 among 3525 patients in the placebo group (mean difference, −1.8 ml per minute per 1.73 m^2; 95% CI, −2.6 to −1.0; P<0.001). Gynecomastia was more common with spironolactone than with placebo, occurring in 81 patients (2.3%) in the spirono-

Table 2. Competing-Risks Analysis of Primary, Secondary, and Safety Outcomes.

Outcome	Spironolactone (N=3537)	Placebo (N=3525)	Hazard Ratio or Odds Ratio*	95% CI†	P Value
Primary outcomes					
Death from cardiovascular causes or new or worsening heart failure — total no. of events (no. per 100 patient-years)	183 (1.7)	220 (2.1)	0.91	0.69–1.21	0.51
Death from cardiovascular causes, myocardial infarction, stroke, or new or worsening heart failure — no. (%)	280 (7.9)	294 (8.3)	0.96	0.81–1.13	0.60
Components of the primary outcomes — no. (%)					
Death from cardiovascular causes	114 (3.2)	116 (3.3)	0.98	0.76–1.27	
Recurrent myocardial infarction	106 (3.0)	107 (3.0)	1.02	0.77–1.35	
Stroke	51 (1.4)	42 (1.2)	1.15	0.72–1.84	
New or worsening heart failure	58 (1.6)	84 (2.4)	0.77	0.51–1.16	
Secondary and safety outcomes — no. (%)					
Death from cardiovascular causes, new or worsening heart failure, or clinically significant arrhythmia‡	173 (4.9)	186 (5.3)	0.95	0.77–1.17	
Clinically significant arrhythmia	20 (0.6)	17 (0.5)	1.45	0.67–3.12	
Death from any cause	166 (4.7)	175 (5.0)	0.95	0.77–1.17	
Death from renal causes, dialysis, renal transplantation, or sustained drop in eGFR of ≥40%	37 (1.0)	44 (1.2)	0.84	0.54–1.30	
Death from renal causes	4 (0.1)	4 (0.1)			
Dialysis or renal transplantation	1 (<0.1)	2 (0.1)			
Persistent drop in eGFR of ≥40%	32 (0.9)	38 (1.1)	0.84	0.52–1.34	
Atrial fibrillation	93 (2.6)	87 (2.5)	1.14	0.84–1.55	

* Numbers are hazard ratios calculated in a competing-risks analysis, except for the composite renal outcome (death from renal causes, dialysis, renal transplantation, or a sustained drop in the estimated glomerular filtration rate [eGFR] of ≥40%) and the persistent drop in eGFR of at least 40%, which are odds ratios calculated with logistic regression.
† The widths of the confidence intervals (CI) have not been adjusted for multiplicity and may not be used in place of hypothesis testing.
‡ Clinically significant arrhythmia was specified as ventricular tachycardia that led to an intervention, including electrical cardioversion, intravenous administration of antiarrhythmic agents, or chest compressions; any ventricular fibrillation; or any cardiac arrest that led to chest compressions, electrical cardioversion, or intravenous administration of antiarrhythmic agents or epinephrine.

lactone group as compared with 19 (0.5%) in the placebo group (P<0.001) (Table 3).

DISCUSSION

After myocardial infarction, treatment with spironolactone, as compared with placebo, did not reduce the incidence of death from cardiovascular causes or new or worsening heart failure or the incidence of composite-outcome events (death from cardiovascular causes, recurrent myocardial infarction, stroke, or new or worsening heart failure) over a median follow-up of 3 years. The incidence of hyperkalemia and gynecomastia was higher with spirononlactone than with placebo.

Previously, the Randomized Aldactone Evaluation Study (RALES) randomly assigned 1663 patients with New York Heart Association functional class III or IV chronic heart failure and reduced ejection fraction (≤35%) to receive spironolactone or placebo.[4] All-cause mortality (the primary outcome) was 30% lower in the spironolactone group than in the placebo group, and the frequency of hospitalization for heart failure was 35% lower in the spironolactone group. EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) randomly assigned 6642 patients with myocardial infarction who had an ejection fraction of less than 40% and either heart failure or diabetes mellitus to receive eplerenone or placebo.[6] Use of eplerenone was associated with a 15% relative risk reduction for both death from any cause and hospitalization for heart failure. In contrast, the

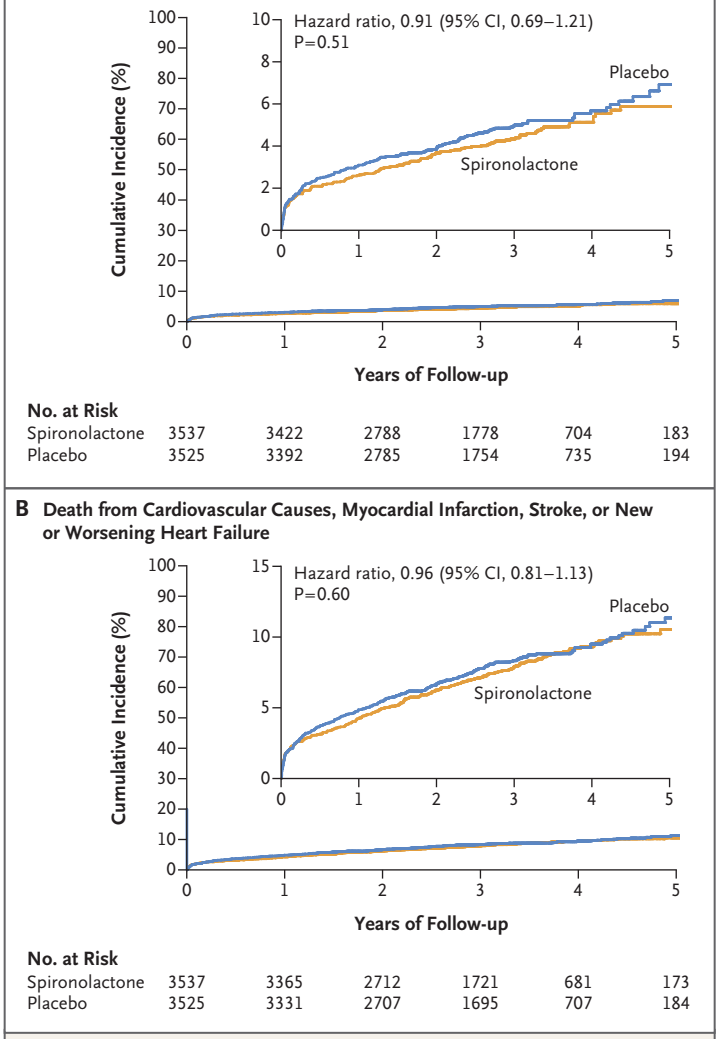

Figure 1. Kaplan–Meier Event Curves for the Primary Outcomes.

Shown are time-to-event curves for the total number of events of death from cardiovascular causes or new or worsening heart failure (Panel A) and the composite of death from cardiovascular causes, myocardial infarction, stroke, or new or worsening heart failure (Panel B). The insets show the same data on an expanded y axis. CI denotes confidence interval.

ALBATROSS (Aldosterone Lethal Effects Blockade in Acute Myocardial Infarction Treated with or without Reperfusion to Improve Outcome and Survival at Six Months Follow-Up) trial randomly assigned 1603 patients with myocardial infarction without heart failure to receive spironolactone or placebo and did not show a reduction in the risk of cardiovascular events with spironolactone. Finally, an additional randomized trial involving patients with STEMI without heart failure showed that eplerenone reduced B-type natriuretic peptide levels, and a meta-analysis suggested benefit from mineralocorticoid antagonists in patients after myocardial infarction without heart failure.[10,15,16]

A recent trial comparing angiotensin receptor–neprilysin inhibitors with an angiotensin-converting–enzyme inhibitor in 5661 patients with myocardial infarction did not show significant reductions in the incidence of death from cardiovascular causes or heart failure.[8] However, an exploratory analysis showed that fewer total cardiovascular events occurred with angiotensin receptor–neprilysin inhibitors than with an angiotensin-converting–enzyme inhibitor.[17] A recent trial of empagliflozin involving 3620 patients with myocardial infarction did not show a reduction in the risk of death or hospitalization for heart failure, but fewer heart failure events occurred with empagliflozin than with placebo.[18] These findings are similar to the findings from our trial and highlight the challenges in improving outcomes after myocardial infarction in the modern era. We did not demonstrate a reduction in mortality with spironolactone. The point estimate for heart failure events in our trial was generally consistent with the findings of previous trials, which reported reductions in heart failure events with spironolactone. The lack of an apparent reduction in cardiovascular mortality may relate to improvements in clinical care over the last two decades, which have resulted in overall lower mortality after myocardial infarction and a reduction in the power of trials to detect meaningful differences. Furthermore, trials of mineralocorticoid antagonists in patients with heart failure and preserved ejection fraction have shown similar findings, with reductions in the incidence of heart failure but no effect on mortality.[5,19] The on-treatment analysis has generated the hypothesis that, with increased adherence to the trial regimen and a lower rate of discontinuation, a benefit may exist; this hypothesis should be tested in future trials.

The newer selective nonsteroidal mineralocorticoid antagonist finerenone has been examined in several trials. In a pooled analysis of two trials comparing finerenone with placebo in 13,026 patients with chronic kidney disease, finerenone was associated with lower incidence of the composite outcome (death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure) (hazard ratio, 0.86;

95% CI, 0.78 to 0.95); a major factor in this result was a reduction in hospitalization for heart failure (hazard ratio, 0.78; 95% CI, 0.66 to 0.92).[20] Furthermore, a randomized trial involving 5734 patients with established renal disease showed that finerenone reduced the risk of the primary composite outcome (renal failure, a sustained decrease from baseline of at least 40% in the eGFR, or death from renal causes) (hazard ratio, 0.82; 95% CI, 0.73 to 0.93).[21] These findings suggest that a selective nonsteroidal mineralocorticoid antagonist can be protective of the kidneys and reduce heart failure.

Our trial has limitations. First, on the basis of the 95% confidence intervals for the primary-outcome results, we cannot exclude a beneficial relative risk reduction of around 30% or smaller, which could be clinically important. Second, despite the increase in sample size, the incidence of events was lower than anticipated, and we cannot rule out type II error due to reduced power. Third, women and members of some racial and ethnic groups were underrepresented in the trial as compared with the incidence of disease in these groups worldwide (Table S6). Fourth, the rate of discontinuation of the trial regimen was higher than anticipated, which may have reduced the power of the trial, especially given the findings of the on-treatment analysis. Fifth, we cannot rule out that the side effects of colchicine in the factorial may have contributed to the discontinuation of spironolactone in the factorial design.

Table 3. Adverse Events.

Event	Spironolactone (N=3537)	Placebo (N=3525)	P Value
	number (percent)		
Any serious adverse event	255 (7.2)	241 (6.8)	0.54
Hyperkalemia leading to discontinuation of trial regimen*	39 (1.1)	20 (0.6)	0.01
Any adverse event	1157 (32.7)	1086 (30.8)	0.09
Hypotension	38 (1.1)	29 (0.8)	0.28
Orthostatic hypotension	16 (0.5)	7 (0.2)	0.06
Breast tenderness	20 (0.6)	2 (0.1)	<0.001
Gynecomastia	81 (2.3)	19 (0.5)	<0.001

* Hyperkalemia was prespecified as a potassium level of greater than 5.5 mmol per liter.

In this trial of spironolactone as compared with placebo in patients with myocardial infarction, spironolactone did not reduce the incidence of a broad composite of cardiovascular outcomes.

Supported by the Canadian Institutes of Health Research, Boston Scientific, and the Population Health Research Institute.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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