

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

APRIL 10, 2014

VOL. 370 NO. 15

Spironolactone for Heart Failure with Preserved Ejection Fraction

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ABSTRACT

BACKGROUND

Mineralocorticoid-receptor antagonists improve the prognosis for patients with heart failure and a reduced left ventricular ejection fraction. We evaluated the effects of spironolactone in patients with heart failure and a preserved left ventricular ejection fraction.

METHODS

In this randomized, double-blind trial, we assigned 3445 patients with symptomatic heart failure and a left ventricular ejection fraction of 45% or more to receive either spironolactone (15 to 45 mg daily) or placebo. The primary outcome was a composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure.

RESULTS

With a mean follow-up of 3.3 years, the primary outcome occurred in 320 of 1722 patients in the spironolactone group (18.6%) and 351 of 1723 patients in the placebo group (20.4%) (hazard ratio, 0.89; 95% confidence interval [CI], 0.77 to 1.04; $P=0.14$). Of the components of the primary outcome, only hospitalization for heart failure had a significantly lower incidence in the spironolactone group than in the placebo group (206 patients [12.0%] vs. 245 patients [14.2%]; hazard ratio, 0.83; 95% CI, 0.69 to 0.99, $P=0.04$). Neither total deaths nor hospitalizations for any reason were significantly reduced by spironolactone. Treatment with spironolactone was associated with increased serum creatinine levels and a doubling of the rate of hyperkalemia (18.7%, vs. 9.1% in the placebo group) but reduced hypokalemia. With frequent monitoring, there were no significant differences in the incidence of serious adverse events, a serum creatinine level of 3.0 mg per deciliter (265 μmol per liter) or higher, or dialysis.

CONCLUSIONS

In patients with heart failure and a preserved ejection fraction, treatment with spironolactone did not significantly reduce the incidence of the primary composite outcome of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure. (Funded by the National Heart, Lung, and Blood Institute; TOPCAT ClinicalTrials.gov number, NCT00094302.)

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This article was updated on April 10, 2014, at NEJM.org.

N Engl J Med 2014;370:1383-92.

DOI: 10.1056/NEJMoa1313731

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MANY PATIENTS WITH HEART FAILURE have a normal or near-normal left ventricular ejection fraction.¹⁻⁴ Such patients share common signs and symptoms, as well as an impaired quality of life and a poor prognosis, with patients who have heart failure and a reduced ejection fraction.⁵⁻⁸ However, the benefit of most medical therapies for heart failure is limited to those with a reduced ejection fraction, generally 40% or less.^{1,2,9} The lack of favorable evidence from clinical-outcome trials involving patients with heart failure and a preserved left ventricular ejection fraction is reflected in current guidelines, which offer no specific recommendations for the management of heart failure in such patients except for attention to coexisting conditions.¹⁰⁻¹²

Among patients with heart failure and a reduced ejection fraction and those with myocardial infarction complicated by heart failure and left ventricular dysfunction, mineralocorticoid-receptor antagonists have been shown to be effective in reducing overall mortality and hospitalizations for heart failure.¹³⁻¹⁵ In small mechanistic studies involving patients with heart failure and preserved left ventricular function, mineralocorticoid-receptor antagonists improved measures of diastolic function.^{16,17} However, their effect on clinical outcomes in such patients has not been rigorously tested. We therefore initiated the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial to determine whether treatment with spironolactone would improve clinical outcomes in patients with symptomatic heart failure and a relatively preserved ejection fraction.^{18,19}

METHODS

STUDY DESIGN AND OVERSIGHT

We designed a phase 3, multicenter, international, randomized, double-blind, placebo-controlled trial. The trial was sponsored by the National Heart, Lung, and Blood Institute. The executive and steering committees designed the trial and oversaw its conduct; the ethics committee at each study site approved the trial design. Data were collected and managed electronically by the New England Research Institutes Clinical Trial Coordinating Center, which also coordinated site monitoring and analyzed the trial results (with independent verification at Brigham and Women's Hospital). The first draft of the manuscript was

written by the first three authors and the last author. All the authors edited and approved the manuscript and assume full responsibility for the accuracy and completeness of the data and for the fidelity of this report to the study protocol, which is available with the full text of this article at NEJM.org. Further details concerning study design and oversight are provided in the Supplementary Appendix, available at NEJM.org.

STUDY PATIENTS

Patients 50 years of age or older were eligible if they provided written informed consent and had at least one sign and at least one symptom of heart failure on a prespecified list of clinically defined signs and symptoms, a left ventricular ejection fraction of 45% or more as measured at the local site by means of echocardiography or radionuclide ventriculography, controlled systolic blood pressure (defined as a target systolic blood pressure of <140 mm Hg or ≤160 mm Hg if the patient was taking three or more medications to control blood pressure), and a serum potassium level of less than 5.0 mmol per liter. In addition, eligible patients had a history of hospitalization within the previous 12 months, with management of heart failure a major component of the care provided (not adjudicated by the clinical-events adjudication committee), or an elevated natriuretic peptide level within 60 days before randomization (a brain natriuretic peptide [BNP] level ≥100 pg per milliliter or an N-terminal pro-BNP [NT-proBNP] level ≥360 pg per milliliter). Trial randomization was stratified according to whether patients were enrolled on the basis of the first criterion (designated the hospitalization stratum) or the second criterion (designated the BNP stratum). The second criterion was considered only for those who did not meet the first criterion.

Exclusion criteria were severe systemic illness with a life expectancy of less than 3 years, severe renal dysfunction (an estimated glomerular filtration rate [GFR] of <30 ml per minute per 1.73 m² of body-surface area or a serum creatinine level that was ≥2.5 mg per deciliter [221 μmol per liter]), and specific coexisting conditions, medications, or acute events.¹⁹ A full list of inclusion and exclusion criteria is provided in the Supplementary Appendix.

RANDOMIZATION AND STUDY DRUGS

Eligible participants were randomly assigned to receive either spironolactone or placebo in a 1:1 ratio with the use of permuted blocks. As

noted above, randomization was stratified according to whether the patient met the criterion for previous hospitalization or BNP elevation. Study drugs were purchased as 15-mg tablets of spironolactone or matching placebo (United Research Laboratories and Mutual Pharmaceutical). Study drugs were initially administered at a dose of 15 mg once daily, which was increased to a maximum of 45 mg daily during the first 4 months after randomization. Subsequent dose adjustments were made as required. Measurement of potassium and creatinine levels was required within 1 week after a change in the study-drug dose and at each scheduled study visit (Fig. S1 in the Supplementary Appendix). Study patients continued to receive other treatments for heart failure and coexisting illnesses throughout the trial. Further details concerning dose adjustments and follow-up assessments are provided in the Supplementary Appendix.

OUTCOMES

The primary outcome was a composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure. All occurrences of the individual components of the primary outcome, as well as myocardial infarctions and strokes, were adjudicated by a clinical end-point committee at Brigham and Women's Hospital according to prespecified criteria; members of the committee were unaware of the study-drug assignments.¹⁸ Other outcomes included death from any cause, hospitalization for any cause, hyperkalemia (potassium level, ≥ 5.5 mmol per liter), hypokalemia (potassium level, < 3.5 mmol per liter), an elevated serum creatinine level (≥ 2 times the baseline value and above the upper limit of the normal range), and a serum creatinine level of 3.0 mg per deciliter (265 μ mol per liter) or higher. A detailed summary of the criteria defining the individual trial-outcome measures reported here is provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

The trial was designed to have 80% power to detect a 20% relative reduction from a 3-year primary outcome rate of 17.4%, with an overall type I error of 0.05 (two-sided test). After accounting for interim monitoring (see the Methods section in the Supplementary Appendix), we calculated that data on 551 participants with primary outcomes confirmed by the clinical end-point committee would be needed to achieve 80% power, and data

on 630 participants with primary outcomes would be needed to achieve 85% power. The target enrollment was 3515 patients.¹⁸

All randomly assigned participants were included in all analyses according to the intention-to-treat principle. For prespecified comparisons of multiple hospitalizations, the planned Poisson regression model was replaced with a negative binomial model to allow for correlated events. All other analyses were prespecified unless stated otherwise. Participants were followed for clinical and laboratory outcomes through their last semianual visit, between January 1, 2013, and June 30, 2013, or until the last contact. For those who withdrew or were lost to follow-up, attempts were made to obtain vital status as of the last potential study visit.

The prespecified primary analysis was a time-to-event analysis with the use of the unadjusted log-rank test. Cox proportional-hazards models were used to obtain unadjusted and covariate-adjusted hazard ratios. Data on participants who did not have a primary-outcome event were censored at the date of last available follow-up information for clinical events. The same approach was used for other time-to-event outcomes. For death from any cause, data were censored on the last date that the participant was known to be alive, which may have been later than the last clinical follow-up. Incidence rates per 100 person-years were also calculated.

Comparisons of recurrent hospitalizations for heart failure and hospitalizations for any cause were performed with the use of negative binomial regression. Longitudinal linear regression methods, without adjustment, were used for laboratory and blood-pressure measurements. A total of 22 prespecified subgroup analyses were conducted for the primary outcome. To assess the homogeneity of study-drug effects across subgroups, we used a Cox proportional-hazards model, including study group, the subgroup variable, and their interaction.²⁰ No adjustments were made for multiple comparisons.

RESULTS

STUDY PATIENTS AND FOLLOW-UP

From August 10, 2006, to January 31, 2012, a total of 3445 participants at 233 sites in 6 countries (1151 participants in the United States, 326 in Canada, 167 in Brazil, 123 in Argentina, 1066 in Russia, and 612 in Georgia) were randomly as-

Table 1. Selected Baseline Characteristics of the Study Patients.*

Characteristic	Spironolactone (N=1722)	Placebo (N=1723)
Age — yr		
Median	68.7	68.7
Interquartile range	61.0–76.4	60.7–75.5
Age ≥75 yr — no. (%)	495 (28.7)	453 (26.3)
Female sex — no. (%)	888 (51.6)	887 (51.5)
White race — no. (%)†	1525 (88.6)	1537 (89.2)
Left ventricular ejection fraction — %		
Median	56	56
Interquartile range	51–61	51–62
NYHA functional classification — no. (%)		
I	56 (3.3)	53 (3.1)
II	1090 (63.3)	1104 (64.1)
III	568 (33.0)	553 (32.1)
IV	7 (0.4)	8 (0.5)
Missing data	1 (<0.1)	5 (0.3)
Eligibility stratum		
Hospitalization in previous year with management of heart failure as major component — no. (%)	1232 (71.5)	1232 (71.5)
Elevated natriuretic peptides in previous 60 days — no. (%)‡	490 (28.5)	491 (28.5)
BNP — pg/ml		
Median	236	235
Interquartile range	149–414	141–410
NT-proBNP — pg/ml		
Median§	887	1017
Interquartile range	537–1634	627–2258
Current smoker — no. (%)	176 (10.2)	184 (10.7)
Blood pressure — mm Hg		
Systolic		
Median	130	130
Interquartile range	120–139	120–140
Diastolic		
Median	80	80
Interquartile range	70–80	70–80
Heart rate — beats/min		
Median	68	68
Interquartile range	62–76	62–76
Body-mass index¶		
Median	31	31
Interquartile range	27–36	27–36
Serum potassium — mmol/liter		
Median	4.3	4.3
Interquartile range	4.0–4.6	4.0–4.6

Table 1. (Continued.)

Characteristic	Spironolactone (N=1722)	Placebo (N=1723)
Serum creatinine — mg/dl		
Median	1.0	1.1
Interquartile range	0.9–1.2	0.9–1.2
Estimated GFR — ml/min/1.73 m ²		
Median	65.3	65.5
Interquartile range	53.9–79.2	53.5–79.1
Hemoglobin — g/dl		
Median	13.2	13.3
Interquartile range	12.1–14.4	12.2–14.5
Region of enrollment — no. (%)		
Americas**	886 (51.5)	881 (51.1)
Russia and Georgia	836 (48.5)	842 (48.9)

* There were no significant differences between the two groups except as indicated. GFR denotes glomerular filtration rate, and NYHA New York Heart Association.

† Race was determined according to self-report.

‡ Patients in this stratum were enrolled on the basis of elevated levels of brain natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP), measured within 60 days before randomization. The study-qualifying BNP or NT-proBNP values were reported in 868 of 981 patients enrolled in this stratum (88.5%); values were not collected for 113 patients (11.5%) who were enrolled before a change to the enrollment form was implemented in August 2007. BNP values were reported for 229 patients in the spironolactone group and 239 patients in the placebo group; NT-proBNP values were reported for 203 patients in the spironolactone group and 197 patients in the placebo group.

§ P=0.04.

¶ The body-mass index was calculated as the weight in kilograms divided by the square of the height in meters.

|| To convert values for creatinine to micromoles per liter, multiply by 88.4.

** The Americas included the United States, Canada, Argentina, and Brazil.

signed to receive spironolactone (1722 participants) or placebo (1723). A total of 2464 participants (71.5%) were enrolled in the hospitalization stratum, and 981 (28.5%) were enrolled in the BNP stratum (Fig. S2 in the Supplementary Appendix). The study groups were balanced with respect to baseline characteristics (Table 1, and Table S1 in the Supplementary Appendix).

The mean follow-up interval was 3.3 years in each study group. A total of 311 participants — 160 in the spironolactone group (9.3%) and 151 in the placebo group (8.8%) — discontinued study participation before the last expected study visit for reasons other than death (Fig. S2 in the Supplementary Appendix). Vital status as of the last expected study visit was unknown for 67 participants in the spironolactone group (3.9%) and 65 participants in the placebo group (3.8%).

STUDY DRUG ADMINISTRATION

The distribution of daily study-drug doses at 8 months after randomization is shown accord-

ing to study group in Table S2 in the Supplementary Appendix. The mean dose at 8 months was 25.0 mg per day in the spironolactone group and 27.7 mg per day in the placebo group. There were 590 participants in the spironolactone group (34.3%) and 541 in the placebo group (31.4%) who permanently discontinued the study drug while continuing to be followed for study outcomes. Tables S3A and S3B in the Supplementary Appendix show the timing of and reasons for early discontinuation of the study drug.

PRIMARY-OUTCOME AND COMPONENT EVENTS

A total of 671 participants had at least one confirmed primary-outcome event: 320 in the spironolactone group (18.6%) and 351 in the placebo group (20.4%). These numbers correspond to incidence rates of 5.9 events per 100 person-years and 6.6 events per 100 person-years, respectively (P=0.14 by the log-rank test). The unadjusted hazard ratio was 0.89 (95% confidence interval [CI], 0.77 to 1.04) (Table 2 and Fig. 1). The inci-

Table 2. Incidence Rates of the Primary Composite Outcome, Its Components, and Additional Secondary Outcomes.*

Outcome	Spironolactone (N=1722)		Placebo (N=1723)		Hazard Ratio with Spironolactone (95% CI)†	P Value
	Participants with Event	Incidence Rate	Participants with Event	Incidence Rate		
	no. (%)	no./100 person-yr	no. (%)	no./100 person-yr		
Primary outcome	320 (18.6)	5.9	351 (20.4)	6.6	0.89 (0.77–1.04)	0.14
Components of the primary outcome						
Death from cardiovascular causes	160 (9.3)	2.8	176 (10.2)	3.1	0.90 (0.73–1.12)	0.35
Aborted cardiac arrest	3 (0.2)	0.05	5 (0.3)	0.09	0.60 (0.14–2.50)	0.48
Hospitalization for heart failure	206 (12.0)	3.8	245 (14.2)	4.6	0.83 (0.69–0.99)	0.04
Additional secondary outcomes						
Death from any cause	252 (14.6)	4.2	274 (15.9)	4.6	0.91 (0.77–1.08)	0.29
Hospitalization for any reason	766 (44.5)	18.8	792 (46.0)	20.0	0.94 (0.85–1.04)	0.25
Myocardial infarction	65 (3.8)	1.2	64 (3.7)	1.1	1.00 (0.71–1.42)	0.98
Stroke	57 (3.3)	1.0	60 (3.5)	1.1	0.94 (0.65–1.35)	0.73

* Some participants had more than one component of the primary outcome and are included once for the primary outcome and once for each component they had.

† Shown are unadjusted hazard ratios calculated with the use of Cox proportional-hazards models.

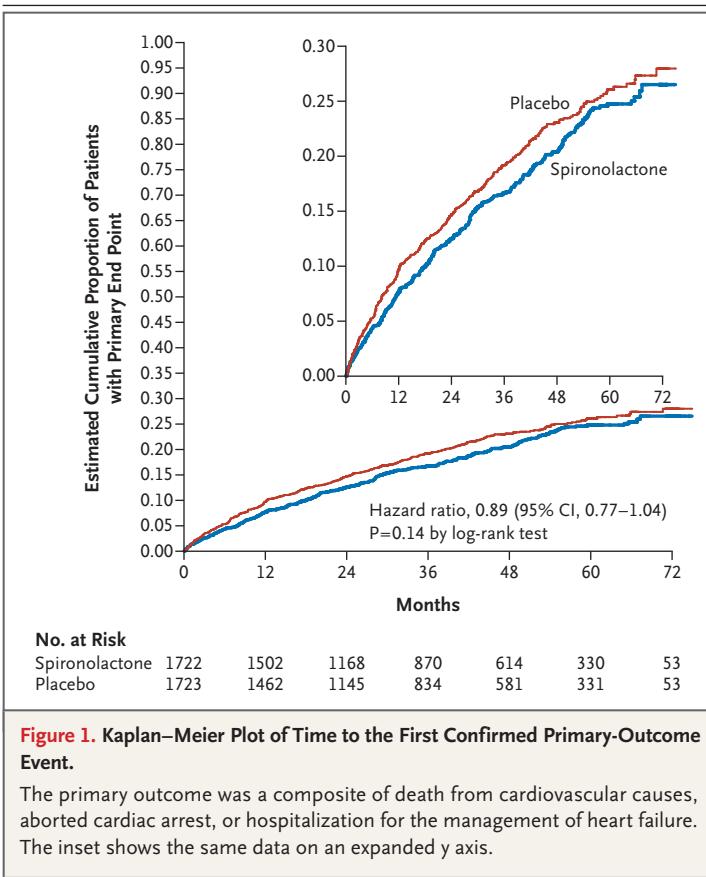


Figure 1. Kaplan–Meier Plot of Time to the First Confirmed Primary-Outcome Event.

The primary outcome was a composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure. The inset shows the same data on an expanded y axis.

dence rates and the adjusted models are shown in Table S4 in the Supplementary Appendix.

Death from cardiovascular causes occurred in 160 patients in the spironolactone group (9.3%) and 176 patients in the placebo group (10.2%), with a hazard ratio of 0.90 (95% CI, 0.73 to 1.12; P=0.35 by the log-rank test) (Fig. 2A). Aborted cardiac arrest occurred in 3 patients in the spironolactone group (0.2%) and 5 patients in the placebo group (0.3%) (P=0.48 by the log-rank test). Hospitalization for heart failure occurred in 206 patients in the spironolactone group (12.0%) and 245 patients in the placebo group (14.2%), with a hazard ratio of 0.83 (95% CI, 0.69 to 0.99; P=0.04 by the log-rank test) (Fig. 2B). Approximately two thirds of first primary-outcome events were hospitalizations for heart failure. In an analysis of total hospitalizations (including repeat hospitalizations) for heart failure over the entire study period, the frequency was lower in the spironolactone group than in the placebo group (394 vs. 475 hospitalizations; 6.8 vs. 8.3 per 100 person-years; P=0.03).

The results of analyses of the primary outcome in 22 prespecified subgroups are shown in Figure S3 in the Supplementary Appendix. Study-drug effects differed significantly only according to randomization stratum (P=0.01 for interac-

tion). In the hospitalization stratum, spironolactone had no effect on the time to the composite outcome (hazard ratio, 1.01; 95% CI, 0.84 to 1.21; $P=0.92$), whereas in the BNP stratum, spironolactone showed a benefit (hazard ratio, 0.65; 95% CI, 0.49 to 0.87; $P=0.003$) (see Table S5A in the Supplementary Appendix for the primary outcome and its components according to randomization stratum). As compared with patients in the hospitalization stratum, patients in the BNP stratum were older; were less likely to be current smokers; had higher baseline creatinine levels, lower potassium levels, and lower estimated GFRs; and were less likely to be enrolled at sites in Russia or Georgia (Table S5B in the Supplementary Appendix).

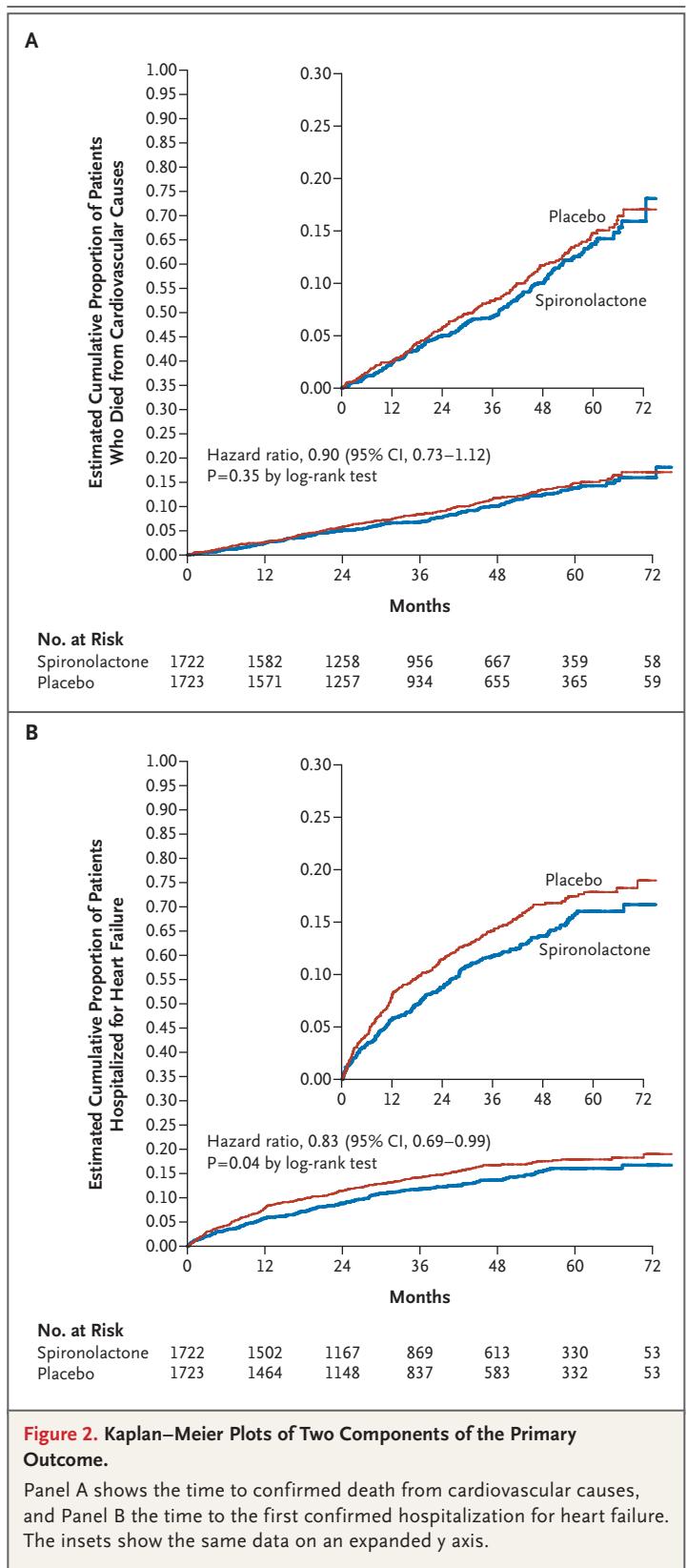
Post hoc analysis indicated marked regional differences in event rates (Table S6 in the Supplementary Appendix). In the Americas (the United States, Canada, Brazil, and Argentina), the primary outcome occurred in 242 patients in the spironolactone group (27.3%) and 280 patients in the placebo group (31.8%). In Russia and Georgia, the primary outcome occurred in 78 patients in the spironolactone group (9.3%) and 71 patients in the placebo group (8.4%). However, the prespecified test for interaction between region and study group was not significant ($P=0.12$) (Fig. S3 in the Supplementary Appendix).

SECONDARY OUTCOMES

There were no significant differences between study groups in time to death from any cause or first hospitalization for any reason (Table 2 and Fig. 3, and Fig. S4 in the Supplementary Appendix). Causes of death were generally similar between the two groups (Table S7 in the Supplementary Appendix). The frequency of hospitalization for any reason (including recurrent hospitalization) did not differ significantly according to study group (36.8 hospitalizations per 100 person-years in the spironolactone group and 36.3 per 100 person-years in the placebo group, $P=0.71$). There were no significant differences in rates of myocardial infarction or stroke between the groups (Table 2).

ADVERSE EVENTS

There were 2395 serious adverse events in the spironolactone group and 2387 in the placebo group (41.6 per 100 person-years and 41.8 per



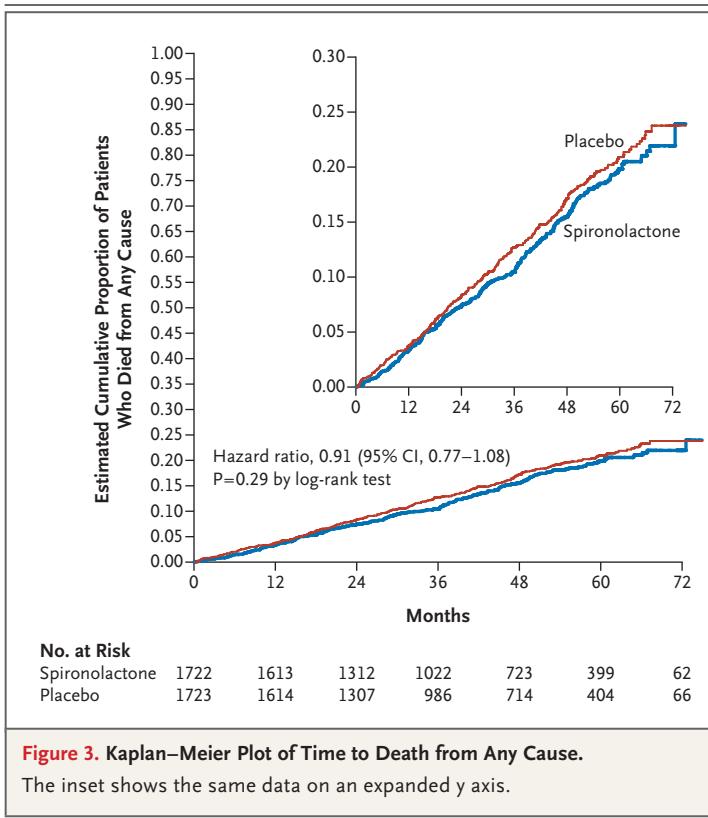


Figure 3. Kaplan–Meier Plot of Time to Death from Any Cause.

The inset shows the same data on an expanded y axis.

100 person-years, respectively). The spironolactone group had a higher rate of hyperkalemia (18.7%, vs. 9.1% in the placebo group) and a lower rate of hypokalemia (16.2% vs. 22.9%). The spironolactone group was more likely to have a doubling of the serum creatinine level to a value above the upper limit of the normal range (10.2% vs. 7.0%). However, there were no significant between-group differences in the proportion of patients with a serum creatinine level of 3.0 mg per deciliter or higher or who required dialysis. Systolic blood pressure at postbaseline visits was significantly lower in the spironolactone group. In addition, discontinuation of the study drug due to breast tenderness or gynecomastia was significantly more frequent in the spironolactone group. A more detailed description of the adverse events is provided in the Supplementary Appendix, including Table S8.

DISCUSSION

The TOPCAT trial was adequately powered for its composite primary outcome of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for heart failure. We found

that adding spironolactone to existing therapy in patients with heart failure and a preserved ejection fraction did not significantly reduce the incidence of the primary outcome.

Neither the time to first hospitalization for any reason nor the time to death from any cause was significantly altered by random assignment to spironolactone. These two inclusive outcome measures are important for assessing overall risk versus benefit but were not anticipated to be significantly reduced by a therapy addressing only one aspect of the broad range of coexisting conditions in this patient population. The incidence rates of death from any cause and of hospitalization for heart failure in our placebo group (4.6 events per 100 person-years for each outcome) are similar to rates observed in other major trials involving patients with heart failure and a preserved ejection fraction²¹⁻²⁵ and are considerably higher than those in trials involving patients with hypertension,²⁶ diabetes,²⁷ or stable coronary artery disease.^{28,29}

In the context of a neutral primary finding, all other secondary analyses should be considered as provisional. However, the individual components of any composite primary end point are always important in interpreting the overall trial result. Death from cardiovascular causes occurred in approximately 10% of patients and did not differ significantly between the study groups. Survival of a documented cardiac arrest occurred in only eight patients. Hospitalization for heart failure was the most common component of the primary outcome, and the rate of this outcome was reduced in the spironolactone group, a finding that was reinforced by the results of a prespecified analysis of cumulative hospitalizations for heart failure.

Of the 22 prespecified subgroups, only the eligibility stratum was associated with a significant treatment interaction. Spironolactone significantly reduced the rate of the primary outcome among patients enrolled on the basis of an elevated natriuretic peptide level but not among those enrolled on the basis of a previous hospitalization for heart failure. This could be a chance finding, given the multiple analyses. However, we noted multiple differences in the baseline characteristics of patients according to stratum. In the placebo group in the TOPCAT trial, there was an unexpectedly lower risk^{30,31} of the primary outcome among those who had been hospitalized previously than among those

who had not (Table S5A in the Supplementary Appendix). In addition, the great majority of patients from Russia and Georgia were enrolled in the hospitalization stratum, whereas patients from the Americas were more evenly balanced between the two strata (Table S5B in the Supplementary Appendix).

These unanticipated observations led to additional, exploratory post hoc analyses. We observed a marked regional variation in event rates, with patients in the placebo group who were enrolled in Russia or Georgia having a much lower likelihood of a primary-outcome event than those enrolled in the Americas (Table S6 in the Supplementary Appendix). This discrepancy in event rates with placebo was unexpected and is unexplained. However, it may reflect regional heterogeneity of coexisting conditions and practice patterns,³²⁻³⁵ including differential use of hospitalization, as well as the clinical challenges in diagnosing heart failure with a preserved ejection fraction.³⁶ The discrepancy in event rates with placebo may have contributed to the observed treatment benefit in the Americas but not in Russia or Georgia (where low event rates would be difficult to reduce further) and the observed treatment benefit among patients enrolled in the BNP stratum but not among those enrolled in the hospitalization stratum (because most of the patients enrolled in Russia and Georgia were in the hospitalization stratum).

The achieved dose of spironolactone in the TOPCAT trial was similar to the mean dose in the Randomized Aldactone Evaluation Study,¹⁴ and dose adjustments were limited by elevations in serum creatinine and potassium levels. Approximately one third of participants discontinued the study drug for these and other reasons, which is an additional important limitation of our trial. There was a significant increase in hyperkalemia and an increase in serum creatinine levels with spironolactone, findings that under-

score the importance of monitoring if spironolactone is used in patients with heart failure and a preserved ejection fraction.

In conclusion, we compared spironolactone with placebo for the treatment of heart failure with a preserved ejection fraction. Spironolactone did not significantly reduce the composite primary end point of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for heart failure.

The content of this article does not necessarily represent the views of the National Heart, Lung, and Blood Institute or of the Department of Health and Human Services.

Supported by a contract from the National Heart, Lung, and Blood Institute, National Institutes of Health (HHSN268200425207C).

Dr. Pitt reports receiving consulting fees from and holding stock and stock options in AuraSense Therapeutics, receiving consulting fees from and holding stock options in Relypsa and BG Medicine, receiving consulting fees from Pfizer, Bayer, AstraZeneca, Amorcey, Mesoblast, Takeda Pharmaceutical, and Gambro, receiving fees for serving on data and safety monitoring boards from Novartis and Johnson & Johnson, receiving fees for serving on a clinical-events committee from Juventas Therapeutics, receiving grant support from Forest Laboratories, and holding a pending patent related to site-specific delivery of eplerenone to the myocardium (14/175,733). Dr. Pfeffer reports receiving consulting fees and grant support from Amgen, consulting fees from Aastrom Biosciences, Abbott Vascular, Cerenis Therapeutics, Concert Pharmaceuticals, FibroGen, GlaxoSmithKline, Medtronic, Merck, Roche, Servier, and Teva Pharmaceuticals, and grant support from Celladon, Novartis, and Sanofi-Aventis and being a coinventor on patents related to the use of inhibitors of the renin-angiotensin system in selected survivors of myocardial infarction, which are licensed to Novartis and Boehringer Ingelheim (5,972,990 and 5,977,160). Dr. Desai reports receiving consulting fees from Novartis, Boston Scientific, Reata Pharmaceuticals, CardioMEMS, 5AM Ventures, Intel, and Relypsa, travel support from Amgen, and tonometry devices from AtCor Medical for use in an ancillary trial and providing expert testimony for Coverys on behalf of the defendant in a malpractice action regarding failure to diagnose heart failure. Dr. Lewis reports receiving grant support from Novartis, Amgen, and Sanofi-Aventis. Dr. O'Meara reports receiving consulting fees, lecture fees, and grant support from Servier, consulting fees and lecture fees from Pfizer, and consulting fees from Novartis. Dr. Shah reports receiving consulting fees from Novartis and Bayer and grant support from Gilead. Dr. Solomon reports receiving consulting fees and grant support from Novartis and consulting fees from Bayer. No other potential conflict of interest relevant to this article was reported.

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

REFERENCES

- Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med* 2006;355:251-9.
- Bhatia RS, Tu JV, Lee DS, et al. Outcome of heart failure with preserved ejection fraction in a population-based study. *N Engl J Med* 2006;355:260-9.
- Redfield MM, Jacobsen SJ, Burnett JC Jr, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA* 2003;289:194-202.
- Fonarow GC, Stough WG, Abraham WT, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. *J Am Coll Cardiol* 2007;50:768-77.
- McMurray J, Ostergren J, Pfeffer M, et al. Clinical features and contemporary management of patients with low and preserved ejection fraction heart failure: baseline characteristics of patients in the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) programme. *Eur J Heart Fail* 2003;5:261-70.
- Lewis EF, Lamas GA, O'Meara E, et al. Characterization of health-related quality of life in heart failure patients with preserved versus low ejection fraction in CHARM. *Eur J Heart Fail* 2007;9:83-91.
- Hoekstra T, Lesman-Leegte I, van

- Veldhuisen DJ, Sanderman R, Jaarsma T. Quality of life is impaired similarly in heart failure patients with preserved and reduced ejection fraction. *Eur J Heart Fail* 2011;13:1013-8.
8. Lam CS, Donal E, Kraigher-Krainer E, Vasan RS. Epidemiology and clinical course of heart failure with preserved ejection fraction. *Eur J Heart Fail* 2011; 13:18-28.
 9. Braunwald E. Heart failure: an update. *Clin Pharmacol Ther* 2013;94:430-2.
 10. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013;128:1810-52.
 11. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology — developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2012;33: 1787-847.
 12. Shah SJ, Gheorghiadu M. Heart failure with preserved ejection fraction: treat now by treating comorbidities. *JAMA* 2008;300:431-3.
 13. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999;341: 709-17.
 14. Zannad F, McMurray JJ, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011;364:11-21.
 15. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;348:1309-21. [Erratum, *N Engl J Med* 2003;348:2271.]
 16. Edelman F, Wachter R, Schmidt AG, et al. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial. *JAMA* 2013;309:781-91.
 17. Mottram PM, Haluska B, Leano R, Cowley D, Stowasser M, Marwick TH. Effect of aldosterone antagonism on myocardial dysfunction in hypertensive patients with diastolic heart failure. *Circulation* 2004;110:558-65.
 18. Desai AS, Lewis EF, Li R, et al. Rationale and design of the treatment of preserved cardiac function heart failure with an aldosterone antagonist trial: a randomized, controlled study of spironolactone in patients with symptomatic heart failure and preserved ejection fraction. *Am Heart J* 2011;162(6):966.e10-972.e10.
 19. Shah SJ, Heitner JF, Sweitzer NK, et al. Baseline characteristics of patients in the treatment of preserved cardiac function heart failure with an aldosterone antagonist trial. *Circ Heart Fail* 2013;6:184-92.
 20. Assmann SE, Pocock SJ, Enos LE, Kasten LE. Subgroup analysis and other (mis)uses of baseline data in clinical trials. *Lancet* 2000;355:1064-9.
 21. Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet* 2003;362:777-81.
 22. Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med* 2008;359:2456-67.
 23. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J. The Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) study. *Eur Heart J* 2006;27:2338-45.
 24. Ahmed A, Rich MW, Love TE, et al. Digoxin and reduction in mortality and hospitalization in heart failure: a comprehensive post hoc analysis of the DIG trial. *Eur Heart J* 2006;27:178-86.
 25. Campbell RT, Jhund PS, Castagno D, Hawkins NM, Petrie MC, McMurray JJ. What have we learned about patients with heart failure and preserved ejection fraction from DIG-PEF, CHARM-Preserved, and I-PRESERVE? *J Am Coll Cardiol* 2012; 60:2349-56.
 26. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002;288:2981-97. [Errata, *JAMA* 2003;289: 178, 2004;291:2196.]
 27. The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008;358:2545-59.
 28. Braunwald E, Domanski MJ, Fowler SE, et al. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N Engl J Med* 2004;351:2058-68.
 29. Fox KM. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003;362:782-8.
 30. Solomon SD, Dobson J, Pocock S, et al. Influence of nonfatal hospitalization for heart failure on subsequent mortality in patients with chronic heart failure. *Circulation* 2007;116:1482-7.
 31. Abrahamsson P, Swedberg K, Borer JS, et al. Risk following hospitalization in stable chronic systolic heart failure. *Eur J Heart Fail* 2013;15:885-91.
 32. Domanski M, Antman EM, McKinlay S, et al. Geographic variability in patient characteristics, treatment and outcome in an international trial of magnesium in acute myocardial infarction. *Control Clin Trials* 2004;25:553-62.
 33. O'Connor CM, Fiuzat M, Swedberg K, et al. Influence of global region on outcomes in heart failure β -blocker trials. *J Am Coll Cardiol* 2011;58:915-22.
 34. Blair JE, Zannad F, Konstam MA, et al. Continental differences in clinical characteristics, management, and outcomes in patients hospitalized with worsening heart failure results from the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan) program. *J Am Coll Cardiol* 2008;52:1640-8.
 35. Pitt B, Zannad F, Gheorghiadu M, et al. Transatlantic similarities and differences in major natural history endpoints of heart failure after acute myocardial infarction: a propensity-matched study of the EPHEUS trial. *Int J Cardiol* 2010;143:309-16.
 36. Paulus WJ, van Ballegoij JJ. Treatment of heart failure with normal ejection fraction: an inconvenient truth! *J Am Coll Cardiol* 2010;55:526-37.

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