Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med 2014;370:1383-92. DOI: 10.1056/NEJMoa1313731

Spironolactone for Heart Failure with Preserved Ejection Fraction

SUPPLEMENTAL APPENDIX

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METHODS

Study Design and Oversight

The TOPCAT Steering Committee (with input by a Protocol Review Committee appointed by the sponsor, the National Health, Lung and Blood Institute - NHLBI) designed the trial and oversaw its conduct, collaborating with the Executive Committee. The sponsor was represented on both Committees. Each study site's ethics committee approved the trial design. Data were collected and managed electronically by the NERI Clinical Trial Coordinating Center (CTCC), which also coordinated all site monitoring.

Independently of data acquisition and management, NERI statisticians provided reports semiannually to an independent DSMB (appointed by and advisory to the sponsor), as well as to the FDA (annually) on behalf of the sponsor. The DSMB had three interim looks at outcome data by treatment arm. Additional safety reports were provided monthly and quarterly to the DSMB Chair.

The trial results were analyzed by CTCC statisticians (with independent replication by a statistician from Brigham and Women's Hospital, Boston, Massachusetts), executing a pre-specified, sponsor-approved statistical analysis plan. The manuscript was drafted by the senior authors, and was subsequently revised and finalized by all the authors. All authors participated in the submission of the manuscript for publication and assume full responsibility for both the accuracy and completeness of the data, as well as for the fidelity of this report to the study protocol (available with the full text of this article at *NEJM.org*).

The protocol specified asymmetric stopping boundaries for the primary outcome, based on an alpha-spending approach with stronger evidence required to stop early for superiority of spironolactone than to stop early for superiority of placebo. The DSMB had three interim looks at the data when 22.5%, 34.6%, and 56.9% of the eventual 671 subjects with confirmed primary outcome events had experienced a confirmed event. The 2-sided p-value needed to declare spironolactone superior at the end of study was calculated by East [East version 5.3, Cytel Inc.] as 0.0498; to declare spironolactone inferior would require $p < 0.0453$.

Study Procedures

A randomization ratio of 1:1 using permuted blocks was employed within each of two design strata (hospitalization within the last 12 months with management of heart failure as a major component, *or* elevated levels of natriuretic peptide measured in the last 60 days). Treatment group assignment was also dynamically balanced across sites (Zelen 1974). Safety laboratory tests and monitoring of potential study outcomes and side effects were continued for each subject until their last scheduled semi-annual study visit, or until study withdrawal or loss to follow-up, regardless of treatment group.

Titration from an initial daily dose of 15mg to 30mg or 45mg, with local safety monitoring of potassium, creatinine, sodium, and chloride levels one week after each dose change, occurred in the first 4 months after randomization. The achieved dose was maintained unless contraindicated by safety monitoring or other pre-specified clinical event (see supplementary figure S1 for the full dosing algorithm).

Participants continued to receive other treatments for heart failure and any other health conditions throughout the trial, as prescribed by their physicians

Both the spironolactone 15 mg tablets and matching placebo were manufactured by URL Mutual Pharmaceutical in Philadelphia, PA, USA in accordance with federal regulations and ICH guidelines for Good Manufacturing Practices. Because the 15mg dose of spironolactone was not previously approved for use, the sponsor held an IND for this trial (Number 71.883).

NERI's CTCC served as the primary liaison to the sites for reporting of study endpoints and was responsible for ensuring the required endpoint-related data and source documents were collected and translated. A 10% sample for re-adjudication was randomly and blindly inserted in the review process by the CTCC and the results reviewed by the CEC at regular meetings to ensure consistency in application of criteria.

Zelen M. The randomization and stratification of patients to clinical trials. *J Chron Dis* 1974; 27:365-375

Inclusion Criteria

In order for a subject to be eligible for inclusion in the trial, all of the following criteria must be met:

1. Male or female; Age 50 years or older;
2. Heart failure as defined in the table below. One symptom must be present at the time of screening and one sign must be present in the last 12 months;
3. Left ventricular ejection fraction (ideally obtained by echocardiography, although radionuclide ventriculography and angiography are acceptable) ≥ 45% (per local reading). The ejection fraction must have been obtained within 6 months prior to randomization and after any MI or other event that would affect ejection fraction;
4. Controlled systolic BP, defined as a target systolic BP < 140 mm Hg. Subjects with BP up to and including 160 mm Hg are eligible for enrollment if on 3 or more medications to control BP.
5. Serum potassium < 5.0 mmol/L prior to randomization;
6. At least one hospital admission in the last 12 months for which heart failure was a major component of the hospitalization. Transient heart failure in the context of myocardial infarction (MI) does not qualify.

   OR

   Brain natriuretic peptide (BNP) in the last 30 days ≥ 100 pg/ml or N-terminal pro-BNP ≥ 360 pg/ml and not explained by another disease entity;
7. Women of child-bearing potential must have a negative serum/urine pregnancy test within 72 hours prior to randomization, must not be lactating, and must agree to use an effective method of contraception during the entire course of study participation.
8. Willing to comply with scheduled visits;
9. Informed consent form signed by the subject.

TABLE. Criteria for Diagnosing Heart Failure

SYMPTOMS (at least one must be present at the time of screening)	**SIGNS (at least one in last 12 mo.)**
■ Paroxysmal nocturnal dyspnea ■ Orthopnea ■ Dyspnea on mild or moderate exertion	■ Any rales post cough ■ Jugular venous pressure (JVP) ≥ 10 cm H2O ■ Lower extremity edema ■ Chest X-ray demonstrating pleural effusion, pulmonary congestion, or cardiomegaly

Exclusion Criteria

If a subject meets any one of the following criteria then he/she is ineligible for enrollment in the trial:

1. Severe systemic illness with life expectancy judged less than three years;
2. Chronic pulmonary disease requiring home O_2, oral steroid therapy or hospitalization for exacerbation within 12 months, or significant chronic pulmonary disease in the opinion of the investigator;
3. Known infiltrative or hypertrophic obstructive cardiomyopathy or known pericardial constriction;
4. Primary hemodynamically significant uncorrected valvular heart disease, obstructive or regurgitant, or any valvular disease expected to lead to surgery during the trial;
5. Atrial fibrillation with a resting heart rate > 90 bpm;
6. Myocardial infarction in past 90 days;
7. Coronary artery bypass graft surgery in past 90 days;
8. Percutaneous coronary intervention in past 30 days;
9. Heart transplant recipient;
10. Currently implanted left ventricular assist device;
11. Stroke in past 90 days;
12. Systolic blood pressure (SBP) > 160 mm Hg;
13. Known orthostatic hypotension;
14. Gastrointestinal disorder that could interfere with study drug absorption;
15. Use of any aldosterone antagonist or potassium sparing medication in last 7 days;
16. Known intolerance to aldosterone antagonists;
17. Current lithium use;
18. Current participation (including prior 30 days) in any other therapeutic trial;
19. Any condition that, in the opinion of the investigator, may prevent the subject from adhering to the trial protocol;
20. History of hyperkalemia (serum potassium ≥ 5.5 mmol/L) in the past six months or serum potassium ≥ 5.0 mmol/L within the past two weeks;
21. Severe renal dysfunction, defined as an estimated glomerular filtration rate (GFR) < 30 ml/min (per the Modification of Diet in Renal Disease (MDRD) 4-component study equation). Subjects with serum creatinine ≥ 2.5 mg/dl are also excluded even if their GFR is ≥ 30 ml/min;
22. Known chronic hepatic disease, defined as aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels > 3.0 times the upper limit of normal as read at the local lab.

End Point Definitions

I. Death classification

The cause of death will be the underlying cause, not the immediate mode of death. The CEC will subclassify all causes of death in the following categories: CV, non-CV, and unknown.

A. CV death

Cardiovascular death is defined as follows:

Fatal MI

Fatal MI may be adjudicated in any one of the following 3 scenarios:

• Death occurring within 14 days after a documented MI in which there is no conclusive evidence to another cause of death. Subjects who are being treated for MI and die as a result of complications of this MI (eg, sudden death, pump failure, or cardiogenic shock) will be classified as having an MI-related death.
• Autopsy evidence of a recent infarct with no other conclusive evidence of another cause of death.
• A fatal MI may be adjudicated for an abrupt death that has suggestive criteria for an infarct but does not meet the strict definition of an MI. The suggestive criteria are as follows:
    - Presentation of chest pain and one of the following:
    - electrocardiographic (ECG) changes indicative of an acute injury;
    - abnormal markers without evolutional changes (eg, subject died before a subsequent laboratory draw); or
    - other evidence of wall motion abnormality

Pump failure

Death occurring within the context of clinically worsening symptoms and/or signs of HF without evidence of another cause of death. If worsening HF is secondary to MI, then MI should be listed as the primary cause of death given that the subject had a MI within 14 days of death (as above).

Sudden death

Death that occurred unexpectedly in an otherwise stable subject. Further sub-classification of sudden death will be as follows:
    - witnessed;
    - last seen ≥1 and <24 hours;

Presumed sudden death

Death that occurred unexpectedly in an otherwise stable subject in which the subject was last seen ≥24 hours before death and circumstances are suggestive of sudden death.

Presumed CV death

Death occurring when the subject was last seen >24 hours before death and presumed CV death.

Stroke

Death occurring after a documented stroke.

Pulmonary embolism

Death occurring after and as a result of a pulmonary embolism.

CV procedure-related

Death occurring during a CV procedure (coronary artery bypass grafting, percutaneous coronary intervention, and other) or as a result of later complications related to the procedure within 15 days. (eg, a patient who had a CABG up to 15 days ago who developed a subsequent MI requiring inotropes and who later died will still be classified as procedural-related death.)

Other CV

Death must be due to a fully documented other CV cause not included above.

B. Non-CV death

If an unequivocal and documented non-CV cause can be established as the primary cause of death, the event will be classified as non-CV. Non-CV deaths will be further classified into the following categories:

A. Infection
B. Malignancy
C. Pulmonary
D. Gastrointestinal
E. Renal
F. Hyperkalemia
G. Accidental
H. Suicide
I. Diabetes
J. Other

C. Unknown death

For cases of death for which there are insufficient data available to determine if the cause was CV or non-CV, the event will be classified as unknown.

II. Nonfatal end point definitions

A. Myocardial infarction

To meet the criteria for the nonfatal end point of MI, the patient must have positive cardiac markers and either ECG changes or clinical presentation as detailed in the table below.

TABLE. Criteria for MI

	Nonprocedural MI	Post-PCI MI	Post-CABG MI
Clinical presentation	Ischemic symptoms (pain, dyspnea, pressure) at rest or accelerated ischemic symptoms, either of which lasts ≥10 min that the investigator determines is secondary to ischemia OR ECG changes consistent with infarction: -New significant Q waves (or R waves in V1-V2) in 2 contiguous leads in the absence of previous LVH or conduction abnormalities - Evolving ST-segment to T wave changes in ≥2 contiguous leads - Development of new left bundle-branch block - ST-segment elevation requiring thrombolytics or PCI	N/A	N/A
ECG criteria		N/A	N/A
Marker criteria*	AND Cardiac markers: -Troponin result is ≥2 × ULN OR -CK-MB ≥2 × ULN If neither troponin nor CK-MB is drawn/available:	Cardiac markers: Within 24 h of the procedure: -Troponin result is ≥3 × ULN OR -CK-MB ≥3 × ULN If neither troponin nor CK-MB is drawn/available: - CK, serial elevation ≥3 × ULN	Cardiac markers: Within 24 h of the procedure: -CK-MB ≥5 × ULN AND ≥50% above the last measurement if last measure was ULN or more. In the absence of cardiac markers, new pathologic Q waves that are persistent at

	-Serial CK, elevation ≥2 × ULN *If troponin is given in ranges, the ULN for MI will be considered the lowest value in the necrosis range.	AND ≥50% above the last measurement if last measure was ULN or more.	discharge or documentation of new wall motion abnormality (other than septal) will meet criteria for post-CABG MI.

N/A, not applicable; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; LVH, left ventricular hypertrophy; ULN, upper limit of normal or upper reference limit.
*CK-MB or troponin preferred.

Recurrent MI: To make the determination whether there is evidence for a reinfarction after an initial MI, the patient must be clinically stable and symptom free for at least 18 hours since the previous event. In addition, the patient should have

a. either chest pain or ECG changes and
b. the appropriate "rise and fall" of cardiac markers (creatine kinase [CK]–MB or troponin only) should be present with a re-elevation of >50% compared with prior marker to provide evidence of a new MI. Creatine kinase–MB is the preferred biomarker.

B. Hospitalization for worsening congestive HF

Unexpected presentation to an acute care facility requiring an overnight (change in calendar day) hospitalization with exacerbation of HF meeting the following criteria:

At least one of the following symptoms:

- Increasing dyspnea on exertion
- Worsening orthopnea
- Paroxysmal nocturnal dyspnea
- Increasing fatique/worsening exercise tolerance
- Altered mental status
- Other, specify

AND

At least 2 of the following signs:

- Peripheral edema
- Elevated jugular venous pressure
- Radiologic signs of HF
- Increasing abdominal distension or ascites
- Pulmonary edema or rales
- Rapid weight gain

• Hepatojugular reflux
• S3 gallop
• Elevated BNP or NT-proBNP
• Other, specify

AND

Requiring treatment:

Treatment with either intravenous diuretics, intravenous vasodilators, intravenous inotropes, mechanical fluid removal (eg, ultrafiltration or dialysis), or insertion of an intraaortic balloon pump for hemodynamic compromise.

C. Stroke

1. A focal neurologic deficit (resulting from a vascular cause involving the central nervous system) of sudden onset that is not reversible within 24 hours (including death) and not due to other readily identifiable cause (ie, brain tumor, trauma).

OR

2. A focal neurologic deficit (resulting from a vascular cause involving the central nervous system) of sudden onset that is reversible within 24 hours and brain imaging clearly documenting a new infarction or hemorrhage (eg, magnetic resonance imaging with diffusion-weighted imaging).

Subclassification of stroke:

Hemorrhagic: when there is documentation of a hemorrhage.

Nonhemorrhagic: when there is documentation a stroke occurred, but a hemorrhage was not documented or seen on examination.

Unknown: when the imaging study is inconclusive whether a hemorrhage was seen.

D. Aborted cardiac arrest

A patient experiences sudden death or cardiac arrest, with or without premonitory HF or MI, and is resuscitated by cardioversion, defibrillation, or cardiopulmonary resuscitation with a meaningful recovery.

This definition excludes known transient losses of consciousness such as seizure or vasovagal episodes that do not reflect significant cardiac dysfunction

RESULTS

Adverse Events

There were 2,395 serious adverse events in the spironolactone group and 2,387 in the placebo group (41.6 and 41.8 per 100 person-years, respectively). The proportion of subjects with at least one serious adverse event, overall and for specific categories of serious adverse events did not differ between groups (Table S8).

The spironolactone group had significantly higher post-baseline potassium values ($p<0.001$). Hyperkalemia was observed in 322 (18.7%) of participants in the spironolactone group compared with 157 (9.1%) in the placebo group, while hypokalemia occurred in 279 (16.2%) of the spironolactone group and 394 (22.9%) of the placebo group (both $p< 0.001$). No deaths related to hyperkalemia were reported.

Doubling of serum creatinine to a value beyond the upper reference limit was more common in patients assigned to spironolactone than placebo [175 (10.2%) vs. 120 (7.0%), respectively, $p<0.001$]. However, there was no significant difference in the proportion of participants with serum creatinine ≥3.0 mg/dL (5.2% in the spironolactone group and 4.9% in the placebo group) or the proportion on dialysis during the study: 19 (1.1%) and 32 (1.9%) in the spironolactone and placebo groups, respectively.

Systolic blood pressure at post-baseline visits was significantly lower in the spironolactone group ($p<0.001$). At the 8 month visit, spironolactone group participants showed a mean decrease from baseline of 2.7 mmHg, compared to a decrease of 0.2 mmHg in the placebo group ($p<0.001$). The mean decreases in diastolic blood pressure were 2.0 and 0.6 mmHg respectively ($p<0.001$). Discontinuation of study drug due to breast tenderness or gynecomastia was significantly greater in the spironolactone group (Table S3b).

Table S1: Additional baseline characteristics by randomized treatment group.[1, 2]

	Spironolactone N = 1722	Placebo N = 1723
Co-morbid Illness		
Coronary artery disease[3]	989 (57.4%)	1034 (60.1%)
Atrial fibrillation	611 (35.5%)	603 (35.1%)
Diabetes mellitus	565 (32.8%)	553 (32.2%)
Insulin-treated	218 (12.7%)	209 (12.2%)
Chronic kidney disease (eGFR[4]<60 ml/min/1.73m^2)	672 (39.0%)	660 (38.3%)
Hypertension	1567 (91.0%)	1580 (91.9%)
Myocardial infarction	444 (25.8%)	449 (26.1%)
PCI or CABG[5]	403 (23.4%)	410 (23.8%)
Dyslipidemia	1011 (58.7%)	1062 (61.7%)
Chronic obstructive pulmonary disease	209 (12.1%)	194 (11.3%)
Stroke	128 (7.4%)	137 (8.0%)
Medications		
Diuretic	1401 (81.4%)	1416 (82.3%)
ACE-I or ARB[6]	1452 (84.3%)	1448 (84.2%)
Beta-blocker	1346 (78.2%)	1330 (77.3%)
Calcium channel blocker	625 (36.3%)	669 (38.9%)
Aspirin	1122 (65.2%)	1128 (65.6%)
Statin	910 (52.8%)	895 (52.0%)
Long acting nitrate	262 (15.2%)	252 (14.7%)
Warfarin	403 (23.4%)	384 (22.3%)

[1] There were no significant differences between the two groups.

[2] All variables are reported as Number (%).

[3] Coronary artery disease includes myocardial infarction, coronary artery bypass graft, percutaneous intervention, or angina pectoris

[4] eGFR –estimated glomerular filtration rate

[5] PCI – Percutaneous coronary intervention, CABG – coronary artery bypass graft

[6] ACE-I-Angiotensin converting enzyme inhibitor, ARB-Angiotensin II receptor antagonist

Table S2. Daily dose of study medication at Month 8 visit. Individuals who had died prior to their Month 8 visit were not included in the table below (see footnote 1). For those who were still on study but missed the Month 8 visit, the most recent prescribed dose is tabulated.

Daily Dose	Spiro N=1689	Placebo N=1676	Total N=3365[1]
• 0 mg[2, 3]	271 (16.0)	221 (13.2)	492 (14.6)
• 15 mg	277 (16.4)	143 (8.5)	420 (12.5)
• 30 mg	889 (52.6)	983 (58.7)	1872 (55.6)
• 45 mg	252 (14.9)	329 (19.6)	581 (17.3)

[1] These totals exclude participants who died before the Month 8 visit (33 in spironolactone group, 47 in placebo group).

[2] Includes 43 in spironolactone group and 40 in placebo group who had permanently withdrawn from the study before the Month 8 visit.

[3] Includes 228 in spironolactone group and 181 in placebo group who permanently stopped study drug or temporarily stopped drug before the Month 8 visit and remained in the study.

Table S3. Early permanent discontinuation of study drug, i.e. participants who permanently discontinued study drug but continued study participation[1]:

a) Timing of permanent study drug discontinuation. Median time before permanently discontinuing study drug for participants with early discontinuation was 1.0 years in the spironolactone group and 1.3 years in the placebo group. Median time for participants who did not permanently discontinue study drug before their last day on study was 3.4 years in both groups;

a)

	N(%) among all randomized individuals		
	Spironolactone N=1722	Placebo N=1723	P-Value[2]
Any early permanent discontinuation of study drug[1]	590(34.3)	541(31.4)	0.074
Time from study entry to early permanent discontinuation			0.005
• < 1 year	292(17.0)	232(13.5)	
• ≥ 1 year but < 2 years	140(8.1)	114(6.6)	
• ≥ 2 year but < 3 years	69(4.0)	81(4.7)	
• ≥ 3 years	89(5.2)	114(6.6)	
• No early permanent discontinuation	1132(65.7)	1182(68.6)	

[1]Does not include subjects who permanently discontinued study drug on their last day enrolled in the study.
[2]P-values from Chi-square test

b) Reasons for permanent study drug discontinuation, among participants who permanently discontinued study drug but continued study participation.

b)

	N(%) among all randomized subjects		
	Spironolactone N=1722	**Placebo N=1723**	**P-Value[3]**
Reasons for permanent discontinuation, among those with early discontinuation[1,2]			
• Persistent hyperkalemia	45(2.6)	17(1.0)	<0.001
• Potassium ≥ 5.5 mmol/L and subject was on lowest dose of study drug	101(5.9)	20(1.2)	<0.001
• Abnormal renal function	67(3.9)	39(2.3)	0.006
• Anaphylactoid reaction or Intolerance[4]	6(0.4)	11(0.6)	0.225
• Breast tenderness or Enlargement[5]	43(2.5)	5(0.3)	<0.001
• Open label use of any aldosterone antagonist or potassium-sparing diuretic	21(1.2)	51(3.0)	<0.001
• Other	369(21.4)	418(24.3)	0.048
• Discontinued in-person study visits at time of permanent study drug discontinuation	125(7.3)	114(6.6)	0.458
○ "Other" only	98(5.7)	96(5.6)	
○ "Other" and 1 or more additional reasons	0	5(0.3)	
○ "Other" not selected	27(1.6)	13(0.8)	

[1]Does not include participants who permanently discontinued study drug on their last day enrolled in the study

[2]More than one reason can be marked

[3]P-value from Chi-square test

[4]None were anaphylactoid reaction

[5]Of the 43 participants in the spironolactone group permanently discontinuing study drug due to breast tenderness or enlargement, 41 were male and 2 were female. Among the 5 participants in the placebo group permanently discontinuing for this reason, 4 were male and 1 was female.

Table S4: Incidence rates by treatment arm and unadjusted and adjusted Cox proportional hazards models, for the primary composite outcome, its components, and other secondary outcomes.

Outcome[1]	Number and % of Participants with Event, and Incidence Rate per 100 person-years		Unadjusted Model HR (S vs. P), 95% CI, p-value	Adjusted Model 1[2] HR (S vs. P), 95% CI, p-value	Adjusted Model 2[2] HR (S vs. P), 95% CI, p-value
	Spironolactone (N = 1722)	Placebo (N = 1723)			
Primary Outcome	320 (18.6%) 5.9 per 100 person-years	351 (20.4%) 6.6 per 100 person-years	0.89 (0.77-1.04) 0.138	0.87 (0.75-1.01) 0.071	0.87 (0.74-1.01) 0.061
Primary Components					
CV Mortality	160 (9.3%) 2.8 per 100 person-years	176 (10.2%) 3.1 per 100 person-years	0.90 (0.73-1.12) 0.355	0.89 (0.72-1.10) 0.278	0.88 (0.71-1.09) 0.253
Aborted Cardiac Arrest	3 (0.2%) 0.05 per 100 person-years	5 (0.3%) 0.09 per 100 person-years	0.60 (0.14-2.50) 0.482	0.56 (0.13-2.37) 0.435	0.58 (0.14-2.44) 0.459
Hospitalization for Heart Failure	206 (12.0%) 3.8 per 100 person-years	245 (14.2%) 4.6 per 100 person-years	0.83 (0.69-0.99) 0.042	0.80 (0.67-0.96) 0.019	0.80 (0.66-0.96) 0.017
Additional Secondary Outcomes					
All-Cause Mortality	252 (14.6%) 4.2 per 100 person-years	274 (15.9%) 4.6 per 100 person-years	0.91 (0.77-1.08) 0.295	0.89 (0.75-1.05) 0.163	0.88 (0.74-1.05) 0.151
All-Cause Hospitalization	766 (44.5%) 18.8 per 100 person-years	792 (46.0%) 20.0 per 100 person-years	0.94 (0.85-1.04) 0.248	0.93 (0.84-1.03) 0.169	0.93 (0.84-1.03) 0.161
Myocardial infarction	65 (3.8%) 1.2 per 100 person-years	64 (3.7%) 1.1 per 100 person-years	1.00 (0.71-1.42) 0.978	0.97 (0.69-1.37) 0.861	0.98 (0.69-1.38) 0.899
Stroke	57 (3.3%) 1.0 per 100 person-years	60 (3.5%) 1.1 per 100 person-years	0.94 (0.65-1.35) 0.733	0.93 (0.64-1.33) 0.674	0.92 (0.64-1.33) 0.669

[1] Some participants experienced more than one component of the primary outcome, and are included once for the primary outcome, and once for each component they experienced.

[2] This analysis includes pre-specified adjustments for age (as a continuous variable), diabetes history at baseline (insulin-treated, not insulin-treated, or no history of diabetes), and whether or not the participant had been hospitalized for heart failure as a major component in the six months prior to enrollment (adjusted model 1) or in the twelve months prior to enrollment (adjusted model 2).

Table S5. Subgroup analyses by randomization stratum:

a) Incidence rates and unadjusted Cox models by randomization stratum and treatment group for the primary composite outcome and its individual components;

a)

Outcome	P-value for interaction term	Enrolled on basis of hospitalization in the past year for which management of heart failure was a major component (N=2464)			Enrolled on basis of natriuretic peptide entry criteria (N=981)		
		Number and % of Participants with Event, and Incidence Rate per 100 person-years		Unadjusted Model	Number and % of Participants with Event, and Incidence Rate per 100 person-years		Unadjusted Model
		Spironolactone (N = 1232)	Placebo (N = 1232)	HR(1 vs. 2), 95% CI, p-value	Spironolactone (N = 490)	Placebo (N = 491)	HR(1 vs. 2), 95% CI, p-value
Primary Outcome	0.01	242 (19.6%) 6.0 per 100 person-years	235 (19.1%) 6.0 per 100 person-years	1.01 (0.84-1.21) 0.923	78 (15.9%) 5.5 per 100 person-years	116 (23.6%) 8.5 per 100 person-years	0.65 (0.49-0.87) 0.003
CV Mortality[1]	0.11	120 (9.7%) 2.8 per 100 person-years	117 (9.5%) 2.8 per 100 person-years	1.01 (0.78-1.31) 0.924	40 (8.2%) 2.7 per 100 person-years	59 (12.0%) 3.9 per 100 person-years	0.69 (0.46-1.03) 0.069
Aborted Cardiac Arrest[1]	NA	1 (0.1%) 0.02 per 100 person-years	5 (0.4%) 0.12 per 100 person-years	0.20 (0.02-1.69) 0.138	2 (0.4%) 0.13 per 100 person-years	0	NA
Hospitalization for Heart Failure[1]	0.09	151 (12.3%) 3.8 per 100 person-years	162 (13.1%) 4.1 per 100 person-years	0.92 (0.73-1.14) 0.440	55 (11.2%) 3.9 per 100 person-years	83 (16.9%) 6.1 per 100 person-years	0.64 (0.46-0.90) 0.011

[1] Components of primary outcome

b) Baseline characteristics by randomization stratum.

b)

	Hospitalized for heart failure during the 12 months prior to randomization N=2464	No hospitalization for heart failure during the 12 months prior to randomization N=981	P-value[1]
Age (years)	67.0 (59.7,73.7)[2]	73.4 (65.1,79.6)	<0.001
Age≥ 75 years old	516 (20.9%)	432 (44.0%)	<0.001
Female	1265 (51.3%)	510 (52.0%)	0.731
White Race	2212 (89.8%)	850 (86.7%)	0.008
LVEF[3] (%)	56.0 (51.0,61.0)	57.0 (51.0,63.0)	0.061
NYHA[4] Functional Classification			
I	77 (3.1%)	32 (3.3%)	0.400
II	1555 (63.2%)	639 (65.3%)	
III	815 (33.1%)	306 (31.3%)	
IV	13 (0.5%)	2 (0.2%)	
Co-morbid Illness			
Coronary artery disease[5]	1504 (61.1%)	519 (53.0%)	<0.001
Atrial fibrillation	787 (32.0%)	427 (43.6%)	<0.001
Diabetes mellitus	810 (32.9%)	308 (31.4%)	0.405
Insulin-treated	312 (12.7%)	115 (11.7%)	0.663
Chronic kidney disease (eGFR[6]<60ml/min/1.73m^2)	907 (36.8%)	425 (43.3%)	<0.001
Hypertension	2278 (92.5%)	869 (88.7%)	<0.001
Myocardial infarction	641 (26.0%)	252 (25.7%)	0.846
PCI or CABG[7]	486 (19.7%)	327 (33.4%)	<0.001
Dyslipidemia	1399 (56.8%)	674 (68.8%)	<0.001
Chronic obstructive pulmonary disease	267 (10.8%)	136 (13.9%)	0.013
Stroke	172 (7.0%)	93 (9.5%)	0.013
Smoking, current	301 (12.2%)	59 (6.0%)	<0.001
Systolic blood pressure (mmHg)	130 (120, 140)	130 (119, 138)	<0.001
Diastolic blood pressure (mmHg)	80 (70, 82)	72 (64, 80)	<0.001
Heart rate (beats/minute)	68 (62, 76)	68 (60, 74)	<0.001
Body mass index (kg/m^2)	31 (27, 36)	31 (27, 35)	<0.001
Serum potassium (mEq/L)	4.3 (4.0,4.6)	4.2 (3.9,4.5)	<0.001
Serum creatinine (mg/dl)	1.0 (0.9,1.2)	1.1 (0.9,1.3)	0.013
eGFR[6] (ml/min/1.73m^2)	66.2 (54.5,79.7)	63.1 (51.3,77.1)	<0.001
Hemoglobin (g/dl)	13.3 (12.2,14.5)	13.1 (12.1,14.2)	0.020
Medications			
Diuretic	2019 (82.0%)	798 (81.4%)	0.633
ACE-I or ARB[8]	2150 (87.4%)	750 (76.5%)	<0.001
Beta-blocker	1899 (77.2%)	777 (79.2%)	0.194
Calcium channel blocker	940 (38.2%)	354 (36.1%)	0.249

Aspirin	1692 (68.8%)	558 (56.9%)	<0.001
Statin	1205 (49.0%)	600 (61.2%)	<0.001
Long acting nitrate	374 (15.2%)	140 (14.3%)	0.491
Warfarin	463 (18.8%)	324 (33.0%)	<0.001
Region of Enrollment[9]			
Americas (USA, CAN, ARG & BRA)	976 (39.6%)	791 (80.6%)	<0.001
Eastern Europe (RUS & GEO)	1488 (60.4%)	190 (19.4%)	

[1] P-values for continuous variables were from a t-test comparing average value between stratum; p-values for categorical variables were from a Chi-square test comparing the distribution between stratum.

[2] All continuous variables are reported as Median (25^{th} percentile, 75^{th} percentile) and all categorical variables are reported as Number (%).

[3] LVEF – Left ventricular ejection fraction

[4] New York Heart Association

[5] Coronary artery disease includes myocardial infarction, coronary artery bypass graft, percutaneous intervention, or angina pectoris

[6] eGFR –estimated glomerular filtration rate

[7] PCI – Percutaneous coronary intervention, CABG – coronary artery bypass graft

[8] ACE-I-Angiotensin converting enzyme inhibitor, ARB-Angiotensin II receptor antagonist

[9] USA-United States of America, CAN-Canada, ARG-Argentina, BRA-Brazil, RUS-Russia, GEO-Georgia

TABLE S6: Detailed unadjusted and adjusted analyses for the primary outcome by region:

a) Incidence rates and unadjusted Cox models by geographic region and treatment group for the primary outcome;

a)

Outcome	Americas (USA CAN ARG BRA) (N=1,767)			Eastern Europe (RUS GEO) (N=1,678)		
	Number and % of Participants with Event, and Incidence Rate per 100 person-years		Unadjusted Model	Number and % of Participants with Event, and Incidence Rate per 100 person-years		Unadjusted Model
	Spironolactone (N = 886)	Placebo (N = 881)	HR(1 vs. 2), 95% CI, p-value	Spironolactone (N = 836)	Placebo (N = 842)	HR(1 vs. 2), 95% CI, p-value
Primary Outcome	242 (27.3%) 10.4 per 100 person-years	280 (31.8%) 12.6 per 100 person-years	0.82 (0.69-0.98) 0.026	78 (9.3%) 2.5 per 100 person-years	71 (8.4%) 2.3 per 100 person-years	1.10 (0.79-1.51) 0.576

b) Hazard ratios from unadjusted and adjusted analysis of the primary TOPCAT outcome, adding region as a post-hoc adjustment.

b)

	Unadjusted Cox Model **Hazard Ratio,** **95% Confidence Interval** **p- value**	**Adjusted Cox Model[1]** **Hazard Ratio,** **95% Confidence Interval** **p- value**	**Adjusted Cox Model[2]** **Hazard Ratio,** **95% Confidence Interval** **p- value**
Spironolactone vs. Placebo	0.89 (0.77-1.04) 0.138	0.87 (0.74-1.01) 0.061	0.85 (0.73-0.99) 0.043
Age (per year)		1.04 (1.03-1.05) <0.001	1.02 (1.01-1.03) <0.001
Diabetes Mellitus			
• **Insulin treated (vs. no DM at baseline)**		3.99 (3.32-4.79) <0.001	2.33 (1.91-2.83) <0.001
• **Not insulin treated (vs. no DM at baseline)**		1.67 (1.38-2.02) <0.001	1.33 (1.09-1.61) 0.004
Enrollment strata (hospitalization stratum versus natriuretic peptide stratum)		1.12 (0.94-1.33) 0.214	1.65 (1.38-1.98) <0.001
Region (Americas vs. Russia, Georgia)			3.96 (3.22-4.88) <0.001

[1] This analysis includes pre-specified adjustments for age (as a continuous variable), diabetes history at baseline (insulin-treated, not insulin-treated, or no history of diabetes), and whether or not the participant had been hospitalized in the twelve months prior to enrollment with management of heart failure as a major component.

[2] This analysis includes the pre-specified adjustments listed above in Footnote 1, as well as, ad hoc, geographic region.

Table S7. Causes of death, as adjudicated by the Clinical Endpoints Committee.

	Spironolactone N=252		Placebo N=274		Total N=526	
	N	**%**	**N**	**%**	**N**	**%**
CV death	160	63.4	176	64.2	336	63.9
• MI	16	6.3	17	6.2	33	6.3
• Pump Failure	28	11.1	39	14.2	67	12.7
• Sudden Death	56	22.2	55	20.1	111	21.1
• Presumed Sudden Death	7	2.8	10	3.6	17	3.2
• Presumed CV death	33	13.1	33	12.0	66	12.5
• Stroke	15	6.0	10	3.6	25	4.8
• Embolism	1	0.4	1	0.4	2	0.4
• CV procedure	1	0.4	5	1.8	6	1.1
• Other	3	1.2	6	2.2	9	1.7
Non-CV death	74	29.4	71	25.9	145	27.6
• Infection	21	8.3	16	5.8	37	7.0
• Malignancy	27	10.7	25	9.1	52	9.9
• Pulmonary	9	3.6	5	1.8	14	2.7
• GI	4	1.6	13	4.7	17	3.2
• Renal	2	0.8	0	0	2	0.4
• Hyperkalemia	0	0	0	0	0	0
• Accidental	4	1.6	4	1.5	8	1.5
• Suicide	0	0	0	0	0	0
• Diabetes	1	0.4	0	0	1	0.2
• Other	6	2.4	8	2.9	14	2.7
Unknown	18	7.1	27	9.9	45	8.6

Table S8: Percentage of participants experiencing at least one Serious Adverse Event, overall and within each category of event.

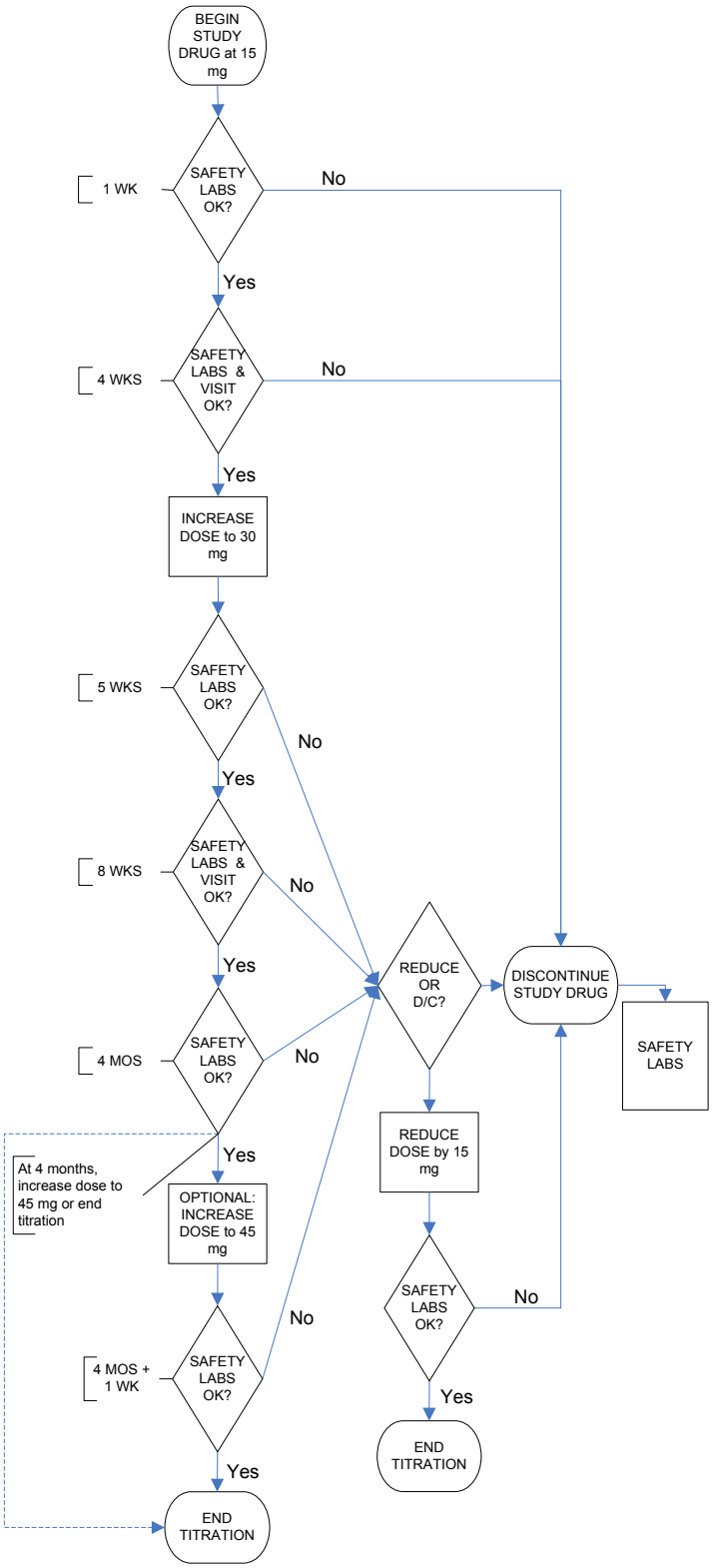
	Spironolactone N = 1722		Placebo N = 1723		
PRIMARY CATEGORY[1]	**N**	**%**	**N**	**%**	**P-Value[2]**
Any Serious Adverse Event	835	48.5	855	49.6	0.517
Auditory/Ocular	13	0.8	11	0.6	0.689
Cancer	53	3.1	50	2.9	0.765
Cardiovascular	578	33.6	566	32.8	0.664
Endocrine and Metabolic	62	3.6	45	2.6	0.096
Gastrointestinal	107	6.2	105	6.1	0.888
Hematological	29	1.7	31	1.8	0.897
Hepatobiliary/Pancreas	22	1.3	25	1.5	0.769
Infection	64	3.7	73	4.2	0.486
Musculoskeletal/Skin	111	6.4	104	6.0	0.623
Neurological/Psychiatric	96	5.6	102	5.9	0.714
Pulmonary/Upper Respiratory	144	8.4	156	9.1	0.506
Renal/Genitourinary	116	6.7	89	5.2	0.052
Sexual/Reproductive Function	6	0.3	7	0.4	1.000
Vascular (non-cardiac)	40	2.3	52	3.0	0.245
Other	97	5.6	108	6.3	0.471

[1]The primary category for each Serious Adverse Event was assigned by the local investigator.

[2]P-value from Fisher's Exact test

Figure S1: Dose titration algorithm and safety assessment schedule

The study drug titration and safety assessment schedule is illustrated in this figure.



Titration: Initial dose: **15 mg/day.** After 4 weeks, the dose should be increased to **30 mg/day** if all safety parameters are acceptable. In the event that the subject continues to have ongoing heart failure symptoms, the investigator has the option to increase the dose to **45 mg/day** at 4 months. Study drug may only be increased after a subject has remained at a constant dose level for 4 weeks. Study drug may not be titrated to less than 15 mg daily or greater than 45 mg daily.

Reduce drug: Reduce the dosing regimen if potassium ≥ 5.5 mmol/L. If the subject is on 45 mg, the dose should be reduced to 30 mg; if the subject is on 30 mg, the dose should be reduced to 15 mg; if the subject is already on the lowest dose (i.e. 15 mg), and if there no alternative explanations for the elevated potassium level (e.g. subjects are taking potassium supplements), the study drug should be permanently discontinued if deemed appropriate by the treating physician and/or TOPCAT Medical Monitors. Once a downward dose adjustment has been made, the study drug should not be uptitrated beyond this level for the trial duration.

Discontinue drug: Permanently discontinue study drug if potassium ≥ 6.0 mmol/L on a non-hemolyzed sample, regardless of the dosing regimen, if there no alternative explanations for the elevated potassium level.

NOTE: Treating physicians may consult the TOPCAT Medical Monitors prior to discontinuing any subjects on study drug as a result of elevated potassium levels. Since there is some room for clinical judgment, subjects could potentially continue to take study drug as long as they are properly monitored. Treating physicians may opt to control a subject's potassium level by adjusting his/her potassium supplement intake (if deemed appropriate and safe) or by recommending a low potassium diet.

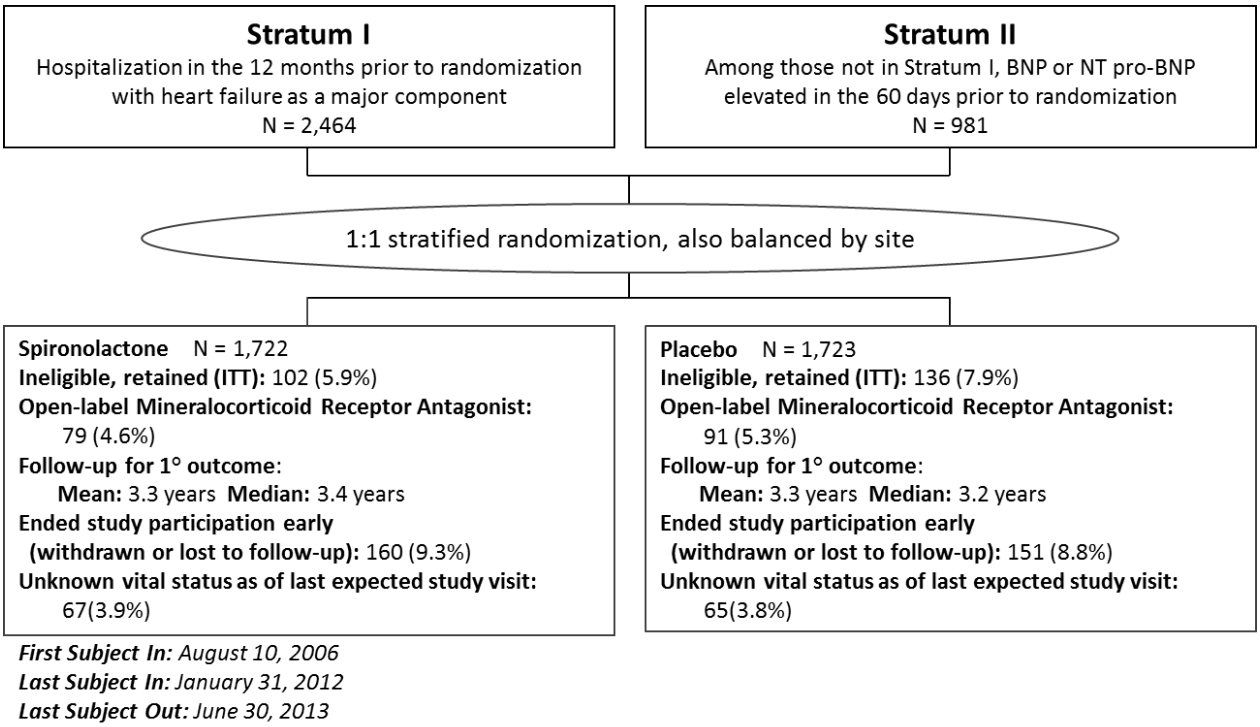
Safety labs: Collect safety labs (i.e., electrolytes and chemistries) at 1 week after each change in the dosing regimen (i.e., either increased, decreased, or stopped).

Reinitiation (after non-compliance): If the dosing regimen is interrupted due to non-compliance, study drug may be reinitiated at the discretion of the treating physician. If a subject is eligible for drug reinitiation, the physician should choose from one the following three options:

- Reinitiate study drug at the highest previously tolerated dose (dose just prior to drug discontinuation); or
- Reinitiate study drug at a lower dose; follow-up labs at 1 week, then resume scheduled study visits if lab work is acceptable; or
- Do not reinitiate study drug

If possible, study drug should be reinitiated within one week of drug discontinuation. The number of times study drug may be reinitiated after non-compliance is at the discretion of the treating physician.

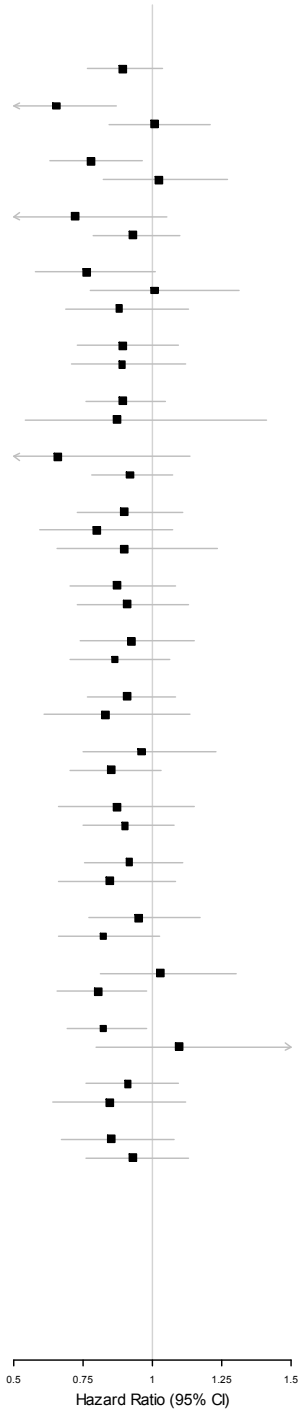
Figure S2: CONSORT diagram. The TOPCAT study did not collect screening data.



First Subject In: *August 10, 2006*
Last Subject In: *January 31, 2012*
Last Subject Out: *June 30, 2013*

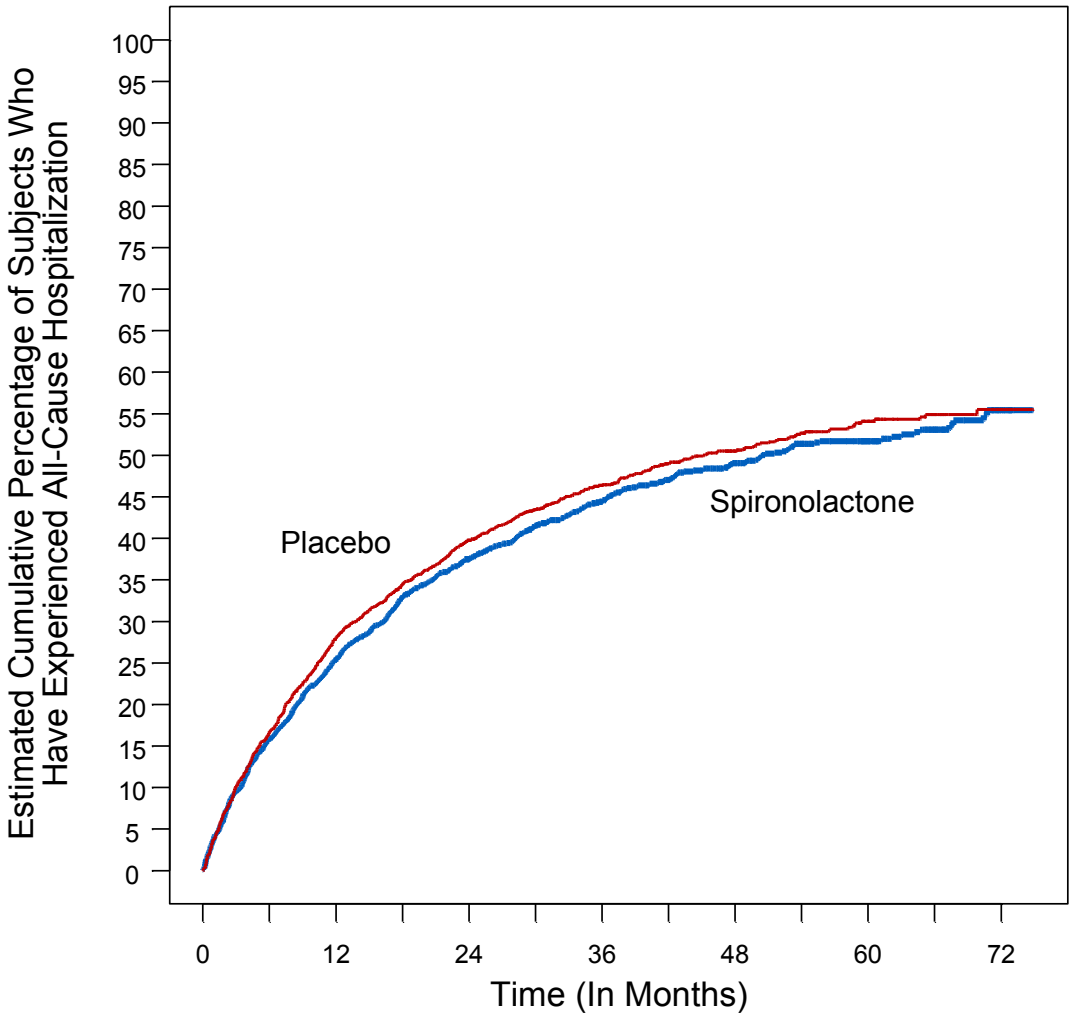
Figure S3: Primary Outcome According to Pre-specified Subgroups.

Subgroup	No. of Events/Patients	Hazard Ratio (95% CI)	P Value for Interaction
All Patients	671/3445 (19.5)	0.89 (0.77-1.04)	
Randomization Stratum			
Not hospitalized for heart failure in the year prior to study enrollment	194/981 (19.8)	0.65 (0.49-0.87)	0.01
Hospitalized for heart failure during that time period	477/2464 (19.4)	1.01 (0.84-1.21)	
Ejection fraction based on local reading			
Less than the median	347/1648 (21.1)	0.78 (0.63-0.96)	0.08
At or above the median	324/1796 (18.0)	1.02 (0.82-1.27)	
Ejection fraction based on local reading			
Less than 50%	112/520 (21.5)	0.72 (0.50-1.05)	0.22
Greater than or equal to 50%	559/2924 (19.1)	0.93 (0.79-1.10)	
Age			
50-64 years	201/1303 (15.4)	0.76 (0.58-1.01)	0.36
65-74 years	223/1194 (18.7)	1.01 (0.78-1.31)	
75 years or older	247/948 (26.1)	0.88 (0.69-1.13)	
Gender			
Male	374/1670 (22.4)	0.89 (0.73-1.09)	0.99
Female	297/1775 (16.7)	0.89 (0.71-1.12)	
Ethnicity			
Non-Hispanic	604/3124 (19.3)	0.89 (0.76-1.05)	0.94
Hispanic	67/321 (20.9)	0.87 (0.54-1.41)	
History of hypertension			
No	52/295 (17.6)	0.66 (0.38-1.14)	0.25
Yes	619/3147 (19.7)	0.92 (0.78-1.07)	
Diabetes mellitus			
No	344/2324 (14.8)	0.90 (0.73-1.11)	0.82
Yes, Insulin-treated	175/427 (41.0)	0.80 (0.59-1.07)	
Yes, Non-insulin-treated	152/691 (22.0)	0.90 (0.65-1.23)	
New York Heart Association congestive heart failure class			
II	323/2194 (14.7)	0.87 (0.70-1.08)	0.80
III & IV	321/1136 (28.3)	0.91 (0.73-1.13)	
Systolic blood pressure			
Less than the median	317/1419 (22.3)	0.92 (0.74-1.15)	0.67
At or above the median	354/2022 (17.5)	0.86 (0.70-1.06)	
Systolic blood pressure			
Less than 140 mm Hg	511/2569 (19.9)	0.91 (0.76-1.08)	0.62
Greater than or equal to 140 mm Hg	160/872 (18.3)	0.83 (0.61-1.14)	
Use of statins			
No	255/1637 (15.6)	0.96 (0.75-1.23)	0.46
Yes	416/1805 (23.0)	0.85 (0.70-1.03)	
Pulse pressure			
Less than the median	198/1117 (17.7)	0.87 (0.66-1.15)	0.85
At or above the median	473/2324 (20.4)	0.90 (0.75-1.08)	
Estimated GFR			
Less than the median	415/1722 (24.1)	0.92 (0.76-1.11)	0.62
At or above the median	256/1723 (14.9)	0.85 (0.66-1.08)	
Estimated GFR			
Less than 60 ml/min/1.73m2	351/1332 (26.4)	0.95 (0.77-1.17)	0.34
Greater than or equal to 60 ml/min/1.73m2	320/2113 (15.1)	0.82 (0.66-1.02)	
BMI			
Less than the median	278/1716 (16.2)	1.03 (0.81-1.30)	0.11
At or above the median	390/1719 (22.7)	0.80 (0.66-0.98)	
Geographic Region			
Americas	522/1767 (29.5)	0.82 (0.69-0.98)	0.12
Eastern Europe	149/1678 (8.9)	1.10 (0.79-1.51)	
Prior Myocardial Infarction			
No	476/2549 (18.7)	0.91 (0.76-1.09)	0.67
Yes	195/893 (21.8)	0.84 (0.64-1.12)	
Heart Rate			
Less than the median	271/1565 (17.3)	0.85 (0.67-1.08)	0.59
At or above the median	399/1875 (21.3)	0.93 (0.76-1.13)	
Racial category*			
White	539/3062 (17.6)		0.98
Black	104/302 (34.4)		
All Other	28/81 (34.6)		
Use of cardiac medication*			
No	2/16 (12.5)		0.94
Yes	669/3426 (19.5)		
Use of blood pressure low ering medication*			
No	2/26 (7.7)		0.94
Yes	669/3416 (19.6)		



* Due to imprecise estimates of the hazard ratio in groups w ith very few events, the hazard ratios, confidence intervals and linear plots are not included if one or more subgroup categories had few er than 50 participants w ith a confirmed event.

Figure S4: Kaplan-Meier plot of time to first hospitalization for any cause (log rank p = 0.248, hazard ratio 0.94, 95% CI 0.85 – 1.04)



Number at Risk								
	Arm 1	1722	1215	841	575	385	223	38
	Arm 2	1723	1162	804	554	372	214	37

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