Journal of the American Heart Association

ORIGINAL RESEARCH

Spironolactone in Atrial Fibrillation With Preserved Cardiac Fraction: The IMPRESS-AF Trial

Eduard Shantsila, PhD; Farhan Shahid, MRCP; Yongzhong Sun, PhD; Jonathan Deeks, PhD; Melanie Calvert, PhD; James P. Fisher, PhD; Paulus Kirchhof, PhD; Paramjit S. Gill, DM; Gregory Y. H. Lip, MD

BACKGROUND: Patients with permanent atrial fibrillation have poor outcomes, exercise capacity, and quality of life even on optimal anticoagulation. Based on mechanistic and observational data, we tested whether the mineralocorticoid receptor antagonist spironolactone can improve exercise capacity, E/e' ratio, and quality of life in patients with permanent atrial fibrillation and preserved ejection fraction.

METHODS AND RESULTS: The double-masked, placebo-controlled IMPRESS-AF (Improved Exercise Tolerance in Heart Failure With Preserved Ejection Fraction by Spironolactone on Myocardial Fibrosis in Atrial Fibrillation) trial (NCT02673463) randomized 250 stable patients with permanent atrial fibrillation and preserved left ventricular ejection fraction to spironolactone 25 mg daily or placebo. Patients were followed for 2 years. The primary efficacy outcome was peak oxygen consumption on cardiopulmonary exercise testing at 2 years. Secondary end points included 6-minute walk distance, E/e' ratio, quality of life, and hospital admissions. Spironolactone therapy did not improve peak oxygen consumption at 2 years (14.0 mL/min per kg [SD, 5.4]) compared with placebo (14.5 [5.1], adjusted treatment effect, −0.28; 95% CI, −1.27 to 0.71]; P=0.58). The findings were consistent across all sensitivity analyses. There were no differences in the 6-minute walking distance (adjusted treatment effect, −8.47 m; −31.9 to 14.9; P=0.48), E/e' ratio (adjusted treatment effect, −0.68; −1.52 to 0.17, P=0.12), or quality of life (P=0.74 for EuroQol-5 Dimensions, 5-level version quality of life questionnaire and P=0.84 for Minnesota Living with Heart Failure). At least 1 hospitalization occurred in 15% of patients in the spironolactone group and 23% in the placebo group (P=0.15). Estimated glomerular filtration rate was reduced by 6 mL/min in the spironolactone group with <1-unit reduction in controls (P<0.001). Systolic blood pressure was reduced by 7.2 mm Hg (95% CI, 2.2–12.3) in the spironolactone group versus placebo (P=0.005).

CONCLUSIONS: Spironolactone therapy does not improve exercise capacity, E/e' ratio, or quality of life in patients with chronic atrial fibrillation and preserved ejection fraction.

REGISTRATION: UTL: https://www.clinicaltrial.gov; Unique identifier: NCT02673463. EudraCT number 2014-003702-33.

Key Words: atrial fibrillation ■ heart failure ■ preserved ejection fraction ■ randomized clinical trial ■ spironolactone

See Editorial by Ho

Patients with permanent atrial fibrillation (AF) have poor outcomes and reduced quality of life even when they receive appropriate stroke prevention therapy and have preserved left ventricular function.[1] The prognosis is worse when maintenance of the sinus rhythm cannot be achieved and the patients progress to persistent or permanent AF, even on optimal rate control.[2]

Correspondence to: Gregory Y. H. Lip, MD, Liverpool Centre for Cardiovascular Science, University of Liverpool, William Henry Duncan Building, 6 West Derby Street, Liverpool L7 8TX, United Kingdom. E-mail: gregory.lip@liverpool.ac.uk or Eduard Shantsila, PhD, Institute of Population Health Sciences, University of Liverpool, Waterhouse Building, Block B, Brownlow Street, Liverpool, L69 3GL, United Kingdom. E-mail: eduard.shantsila1@nhs.net

Supplementary Materials for this article are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.016239

For Sources of Funding and Disclosures, see page 9.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- The study presents a randomized placebo controlled clinical trial of spironolactone versus placebo in patients with chronic atrial fibrillation and preserved ejection fraction.
- Spironolactone therapy does not improve exercise capacity, endothelial function assessed as echocardiographic E/e' ratio, or quality of life in the tested population.

What Are the Clinical Implications?

- The trial does not support use of spironolactone therapy in patients with chronic atrial fibrillation and preserved ejection fraction.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
BP	blood pressure
IMPRESS-AF	Improved Exercise Tolerance in Heart Failure With Preserved Ejection Fraction by Spironolactone on Myocardial Fibrosis in Atrial Fibrillation
MLWHF	Minnesota Living with Heart Failure
NIHR	National Institute for Health Research
VO_{2peak}	peak oxygen consumption

The mechanisms leading to reduced exercise capacity, related morbidity, and mortality in anticoagulated patients with permanent AF are likely related to disturbed diastolic ventricular function, myocardial fibrosis, and stiffening.[3,4] In fact, activators of fibroblast signaling such as fibroblast growth factor 23 are elevated in patients with chronic AF.[5] These changes can lead to ventricular filling abnormality, reducing cardiac output, and decreasing exercise capacity.[3,4] Aldosterone increases cardiac collagen deposition and left ventricular fibrosis.[6] This involves direct stimulation of cardiac fibroblasts by aldosterone to produce collagen with chronification of oxidative stress and inflammation in the heart.[7,8] Cardiac expression of mineralocorticoid receptors is increased in AF, thus augmenting the genomic effects of aldosterone.[9] According to a substudy of the RALES (Randomized Aldactone Evaluation Study) trial, the improved survival in patients with heart failure with impaired cardiac contractility treated by spironolactone was linked to its ability to reduce serum markers of ongoing fibrosis.[10] The recently published RACE-3 (Routine Versus Aggressive Upstream Rhythm Control for Prevention of Early Persistent Atrial Fibrillation in Heart Failure Study), reporting a complex intervention that included spironolactone (>75% difference in use between groups) suggested beneficial effects compared with usual care in patients with recent onset AF.[11]

The IMPRESS-AF (Improved Exercise Tolerance in Heart Failure With Preserved Ejection Fraction by Spironolactone on Myocardial Fibrosis in Atrial Fibrillation) trial therefore tested the effects of mineralocorticoid receptor inhibition with spironolactone in patients with permanent AF with preserved left ventricular ejection fraction compared with placebo on exercise capacity (primary outcome); and its effect on quality of life, diastolic function, all-cause hospital admissions, and spontaneous cardioversion to sinus rhythm (secondary outcomes).

METHODS

The data that support the findings of this study will be made available, provided the request is scientifically sound and from an appropriately qualified research group. All requests for data should be addressed to the corresponding authors.

The IMPRESS-AF trial is a double-masked randomized placebo-controlled multicenter enrollment single-site management trial conducted in Birmingham, United Kingdom. The trial randomized 250 patients with permanent AF and preserved left ventricular function 1:1 to either spironolactone or placebo. Permanent AF was defined as at least 1-year history of AF on all prescreening assessments with a previous decision to the accept rate control strategy and with further confirmation of AF on ECG at the screening. The previously published trial protocol was developed following the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement and the latest PRO-specific guidance.[12,13] The study was approved by the National Research and Ethics Committee West Midlands—Coventry and Warwickshire (REC Reference 14/WM/1211). All patients provided signed informed consent. The study is registered at EudraCT number 2014-003702-33 and Clinicaltrial.gov (NCT02673463). Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the University of Birmingham.

Patients were recruited from primary care general/family practices and outpatient AF clinics in Sandwell

and West Birmingham Hospitals Trust, Birmingham. The patients were ≥50 years with permanent AF, left ventricular ejection fraction ≥55%, and controlled blood pressure (BP).[14] An interpreter and translated materials were available if English was not their preferred language. The exclusion criteria (full list published previously[13]) included life expectancy of <2 years, severe chronic obstructive pulmonary disease, severe mitral or aortal valve stenosis or regurgitation, rapidly progressing or severe renal impairment, potassium ≥5mmol/L, recent coronary artery bypass graft surgery (within 3 months), use of aldosterone antagonist or potassium sparing diuretic within 14 days. All patients received optimized treatment following established clinical guidelines on management of AF, heart failure, and hypertension.[15]

All patients were screened, investigated, and managed in the Research Clinic in the Institute of Cardiovascular Sciences, City Hospital, Birmingham. During the baseline visit, eligible patients underwent cardiopulmonary exercise testing using a cycling ergometer to measure peak oxygen consumption (VO_{2peak}), 6-minute walk test, and completed paper-based quality of life questionnaires (validated Minnesota Living with Heart Failure[16] and EuroQol-5 Dimensions, 5-level version quality of life[17] questionnaires). A block randomization (block size of 4) was performed after the assessments using a secure web-based randomization system. Patients were stratified by their baseline VO_{2peak} of ≤16 and >16 mL/min per kg. Patients, the trial team, care providers, outcome assessors, and data analysts were masked to the treatment allocation. Patients attended the research clinic every 3 months for follow-up (Table S1). The day-to-day management of the trial was coordinated by the Birmingham Clinical Trials Unit, registered by the National Institute for Health Research (NIHR) as a trials unit. A Trial Steering Committee was responsible for overseeing the progress of the trial. An independent Data Monitoring and Ethics Committee was responsible for the regular monitoring of trial data and adverse events.

Patients randomized to spironolactone received 25 mg once daily for 2 years. In the case of an increase in potassium level to 5.1 to 5.5 mmol/L or non-life-threatening side effects (eg, gynecomastia) the dose was down-titrated to 25 mg each second day with an attempt to re-up-titrate the dose if the reason for down-titration has resolved. When potassium levels exceeded 5.5 mmol/L or if toxicity was suspected, the trial medication was stopped for the duration of the trial, but the patients were requested to attend the remaining follow-up visits and their outcomes were included in the intention-to-treat analysis. Patient compliance to treatment was defined adequate when ≥80% of allocated capsules were taken.

The primary hypothesis was assessed by the difference between trial groups in VO_{2peak} on cardiopulmonary exercise testing[18,19] at 2 years, adjusted for the baseline values. The Secondary efficacy end points were 6-minute walk test distance, quality of life using Minnesota Living with Heart Failure, and EuroQol-5 Dimensions questionnaires, diastolic function assessed by E/E' ratio[20,21] on echocardiography, rates of all-cause hospital admissions and spontaneous return to sinus rhythm on ECG. Prespecified safety outcomes were occurrence of breast pain or swelling, allergic reaction, raised serum creatinine (>220 μmol/L), low estimated glomerular filtration (<30 mL/min per 1.73m^2), and hyperkalemia (≥5.1 and ≥6.0 mmol/L).

Statistical Analysis

All primary analyses followed modified intention to treat principles including all patients reporting outcomes regardless of their compliance with the medication. For the primary outcome patients who died before the 2-year follow-up assessment were additionally included with VO_{2peak} scores at 2 years imputed as 0 regardless of cause; 3 sensitivity analyses were undertaken for the primary outcome (further details are available in Data S1). Further analyses included additional adjustments for age, sex, and body mass index at baseline. Predefined subgroup analyses compared the difference in primary outcome VO_{2peak} between spironolactone and placebo according to VO_{2peak}; age, sex, body mass index, systolic and diastolic BP. Details of the statistical methodology for the secondary outcome measures are available in Data S1. Analyses of the study outcomes were defined in a statistical analysis plan, signed off before unmasking. Results are presented in accordance with CONSORT and CONSORT PRO.[22] STATA version 12 software was used for all analyses.

Sample Size

Sample size was determined to be able to show a clinically important difference in the primary outcome of VO_{2peak}. Published values of VO_{2peak} in subjects with heart failure give baseline values (mean 16 [SD 5] mL/min per kg).[23] A difference of 2 mL/min per kg was judged to be clinically relevant. A sample size of 100 patients in each arm would give the power of at least 80% to detect differences in primary and secondary end points of a magnitude consistent with published results from similar studies. We increased the sample size to 125 per arm for provision for a 20% dropout rate. Statistical power would be higher with the benefits of adjusting for baseline values.

Table 1. Baseline Characteristics

	Spironolactone (n=125)	Placebo (n=125)
Demographic characteristics		
Age, y	73 (68–77)	72 (67–78)
Sex		
Women	28 (22%)	31 (25%)
Men	97 (78%)	94 (75%)
Ethnicity		
White	118 (94%)	118 (94%)
Black	3 (2%)	3 (2%)
Asian	3 (2%)	2 (2%)
Ethnicity other than White, Black, or Asian or mixed ethnicity of White, Black and/or Asian background	1 (1%)	2 (2%)
Smoker		
Current smoker	6 (5%)	8 (6%)
Ex-smoker	66 (53%)	68 (54%)
Never smoked	53 (42%)	49 (39%)
Alcohol use, units/wk	3 (0–12)	6 (0–14)
Characteristics of the study outcomes		
VO_{2peak}, mL/kg per min	14 (11–18)	14 (11–18)
VO_{2peak} of ≤16 mL/kg per min	77 (62%)	78 (62%)
6-min walk test, m	266 (196–316)	271 (200–330)
E/E' ratio	9.8 (8.0–12.0)	9.7 (7.5–13.0)
E/E' ratio categories		
<10	66 (52.8%)	64 (51.2%)
≥10 to <14	41 (32.8%)	39 (31.2%)
≥14	18 (14.4%)	22 (17.6%)
EQ-5D-5L		
Score	0.84 (0.74–0.94)	0.88 (0.74–0.94)
Missing data	4 (3%)	5 (4%)
MLWHF score		
Score	7.0 (6.3–35.8)	14.0 (5.8–30.0)
Missing data	8 (6%)	4 (3%)
Clinical characteristics		
Left ventricular ejection fraction (%)	58 (57–62)	58 (56–63)
Brain natriuretic peptide, pg/mL	122 (73–230)	136 (82–241)
Brain natriuretic peptide >130 ng/L	56 (44.8%)	66 (52.8%)
Body mass index, kg/m^2	29 (26–33)	30 (26–34)
Systolic blood pressure, mm Hg	130 (117–140)	129 (118–142)
Diastolic blood pressure, mm Hg	75 (67–83)	74 (68–82)
Resting heart rate, bpm	85 (74–99)	83 (74–97)
Diabetes mellitus	24 (19%)	21 (17%)
Medications		
Non-vitamin K oral anticoagulants	60 (48%)	57 (46%)
Vitamin K antagonists	47 (38%)	47 (38%)
Aspirin	10 (8%)	9 (7%)
Clopidogrel	6 (5%)	4 (3%)
Loop diuretic	25 (20%)	24 (19%)
Thiazide diuretic	14 (11%)	20 (16%)
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker	67 (54%)	80 (64%)
Calcium channel blocker	43 (34%)	37 (30%)
Beta blocker	66 (53%)	70 (56%)
Digoxin	26 (21%)	23 (18%)
Amiodarone	0 (0%)	1 (1%)
Statin	88 (70%)	69 (55%)
Inhalers of asthma or COPD	20 (16%)	17 (14%)

Continuous data presented as median (interquartile range). To score Minnesota Living with Heart Failure questionnaire, it was allowed that at most 20% of 21 responses were missing which was equivalent to 4 data items. If there were ≤4 data items missing then we used mean substitution to impute the missing responses and then scored the questionnaire by summating the responses to all 21 questions; otherwise, the person's score was left missing. EQ-5D-5L indicates EuroQol-5 Dimensions, 5-level version quality of life questionnaire; COPD, chronic obstructive pulmonary disease; MLWHF indicates Minnesota Living with Heart Failure; and VO_{2peak}, peak oxygen consumption.

RESULTS

A total of 250 patients were randomized to spironolactone or placebo (125 per group). Patients were elderly (mean age, 72.3 [SD, 7.4] years, further details in Table 1). Random groups were well balanced (Table 1). The final study visit was attended by 101 (81%) patients randomized to spironolactone and 106 (85%) randomized to placebo (Figure 1). Spironolactone had the expected effect on BP and kidney function. Systolic BP was reduced by 7.2 mm Hg (95% CI, 2.2–12.3) in the spironolactone group, almost no change in the placebo group (Table S2). There was no significant treatment effect for diastolic BP. Spironolactone increased creatinine (mmol/L) by 6.9 (95% CI, 3.4–10.5) and lowered estimated glomerular filtration rate (mL/min per 1.73) by 6.0 (95% CI, −9.3 to −2.8) at 2 years.

Data on the primary outcome, VO_{2peak} at the end of the trial were available for 106 patients in placebo group and 103 patients in spironolactone group (Table 2), which included 3 deaths in placebo group and 5 deaths in spironolactone group. In both groups, 3 patients were not able to perform cardiopulmonary exercise testing because of frailty. In the primary intention to treat analysis, VO_{2peak} (mL/min per kg) changed from mean 14.5 (SD 4.6) to mean 14.0 (SD 5.4) in the spironolactone group and from mean 14.6 (SD, 5.1) to mean 14.5 (SD, 5.1) in placebo group. The treatment effect showed no difference between the groups (differences in mean −0.28, 95% CI, −1.27 to 0.71; *P*=0.58). The findings were

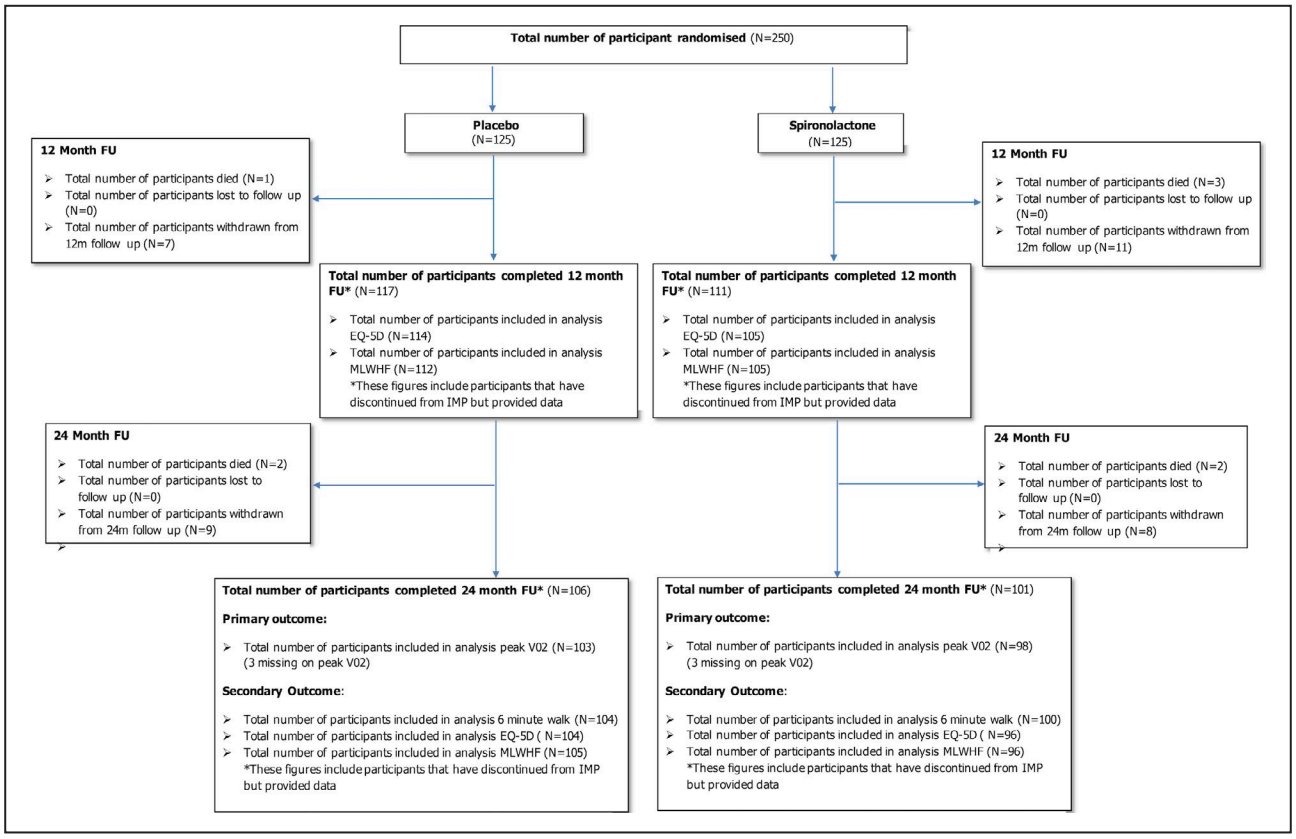

Figure 1. CONSORT flow diagram.
EQ-5D indicates EuroQol-5 Dimensions, 5-level version quality of life questionnaire; FU, follow up; IMP, investigational medicinal product; and MLWHF, Minnesota Living with Heart Failure.

consistent across the performed sensitivity analyses (Table 2, Table S3).

The subgroup analyses showed no significant interaction of treatment with baseline VO_{2peak} values (mL/min per kg, ≤16 versus >16, *P*=0.54), body mass index (kg/m^2, <25 versus 25–30 versus ≥30, *P*=0.13), sex (*P*=0.91), median BP (*P*=0.36 for systolic BP and *P*=0.93 for diastolic BP), and E/E' ratio (<10 versus 10–14 versus ≥14, *P*=0.73) (Table 3). There was a significant interaction between treatment and age: higher VO_{2peak} values were observed in older patients randomized to spironolactone, but in younger patients in placebo group (*P*=0.03 for interaction). The magnitude of the differences was small, with the point estimates for the treatment effect in each subgroup being smaller than the pre-stated clinically important treatment effect.

There was no difference between random groups in any of the secondary outcomes (Table 2, Table S4). The findings remained consistent after adjustment of age, sex, and body mass index for all outcomes (Tables S3 and S4). Spontaneous return to sinus rhythm on ECG performed at 2 years was uncommon in both study groups (4 [4%] in placebo group and 8 [8%] in spironolactone group, *P*=0.21) (Table 4, Table S5). At least 1 hospitalization was observed in 15% of patients in spironolactone group and 23% in placebo group (hazard ratio, 0.65; 95% CI, 0.36–1.17) (Table 4, Figure 2, Table S5). There was no significant difference in overall mortality, death from cardiac causes, hospitalizations because of cardiac causes, and rates of stroke and systemic thromboembolism between the study arms (Tables S6 through S8). Patients in the spironolactone group had a higher occurrence of breast pain (17 versus 5 in controls), breast swelling (11 versus 4 in controls), and hyperkalaemia (≥5.1 mmol/L, 46 versus 17 in controls) (Table S6).

DISCUSSION

Mechanistic studies have demonstrated that elevation in cardiac filling pressures (estimated by E/e' in this trial) contributes to pulmonary limitations and impaired VO_{2peak}.[24,25] Treatment with spironolactone in the IMPRESS-AF study does not improve either exercise capacity or quality of life in this cohort of stable patients with permanent AF with preserved ejection fraction despite lowering BP. CIs excluded clinically important effects. On the contrary, kidney function,

Table 2. Study Outcomes

	Spironolactone		Placebo		Treatment Effect*	
	Mean (SD)	n	Mean (SD)	n	(95% CI)†	*P* Value*
Primary outcome†						
VO_{2peak}, mL/kg per min	14.0 (5.4)	103	14.5 (5.1)	106	−0.28 (−1.27 to 0.71)	0.58
Primary outcome sensitivity analysis						
Per protocol analysis:‡ VO_{2peak}, mL/kg per min	14.8 (4.3)	57	14.9 (4.9)	77	0.21 (−0.78 to 1.21)	0.67
Complete case analysis: VO_{2peak}, mL/kg per min	14.8 (4.5)	98	14.9 (4.6)	103	−0.09 (−0.86 to 0.68)	0.81
Multiple imputation method:§ VO_{2peak}, mL/kg per min	13.4 (6.0)‖	125	14.0 (5.5)‖	125	−0.53 (−1.57 to 0.51)	0.32
Adjusted for stratification variable and BNP level: VO_{2peak}, mL/kg per min	14.0 (5.4)	103	14.5 (5.1)	106	−0.32 (−1.31 to 0.68)	0.53
Analysis removing patients who died and could not perform CPET (assigned to a peak VO_2 of 0) at follow-up: VO_{2peak}, mL/kg per min¶	14.8 (4.6)	98	14.9 (4.6)	103	−0.09 (−0.86, 0.68)	0.81
Secondary outcomes						
6-min walk test distance, m†	313 (108)	105	330 (112)	107	−8.47 (−31.9 to 14.9)	0.48
E/E′ ratio	9.00 (3.05)	101	9.72 (3.57)	106	−0.68 (−1.52 to 0.17)	0.12
Brain natriuretic peptide, pg/mL	179 (171)	101	186 (110)	105	4.95 (−28.3 to 38.2)	0.77
EQ-5D-5L score†	0.81 (0.26)	98	0.84 (0.21)	104	−0.008 (−0.06 to 0.04)	0.74
MLWHF score#	17.4 (22.7)	96	15.3 (20.4)	104	0.49 (−4.32 to 5.29)	0.84

BNP, brain natriuretic peptide; CPET indicates cardiopulmonary exercise testing; EQ-5D-5L, EuroQol-5 Dimensions, 5-level version quality of life questionnaire; MLWHF, Minnesota Living with Heart Failure; $VO_{2peak,}$ peak oxygen consumption.

*The mean differences between the spironolactone group and placebo group, 95% CIs, and the corresponding *P* values were estimated from linear regression models adjusting for the baseline continuous peak oxygen consumption score. In the sensitivity analyses additional adjustments were made for age, sex, and body mass index.

†A value of 0 was assigned to peak oxygen consumption, 6-minute walk test, and EuroQol-5 Dimensions, 5-level version quality of life questionnaire scores for those who died.

‡Per-protocol population was defined as ≥80% of capsules taken.

§Predictive Mean Matching imputation method was used to generate 20 imputed data sets. Data for participants in spironolactone group and placebo group were imputed separately. peak oxygen consumption, age, body mass index, systolic/diastolic blood pressure, 6-minute walk test, brain natriuretic peptide level, E/E' ratio, EuroQol-5 Dimensions, 5-level version quality of life, Minnesota Living with Heart Failure scores at baseline and sex were included in the imputation model.

‖SD estimates were obtained by multiplying the standard error by the square root of 125.

¶Total of 8 exclusions; 5 from spironolactone, and 3 from placebo.

#For Minnesota Living with Heart Failure questionnaire, score ranges from 0 to 105 with a higher score reflecting poorer quality of life; the highest value across the whole participants was assigned to those who died. All patients choose to use the English version of the questionnaires with only 1 proxy completion case recorded (placebo group is the reference group).

assessed by estimated glomerular filtration rate, worsened in patients randomized to spironolactone.

Clinical trials of the aldosterone antagonists spironolactone and eplerenone (RALES, EPHESUS [Eplerenone Post-AMI Heart Failure Efficacy and Survival Study], EMPHASIS-HF [Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study]) uniformly showed their clinical benefits in systolic heart failure. The IMPRESS-AF study conclusively demonstrates that use of an aldosterone antagonist, spironolactone does not improve aerobic capacity, estimated filling pressures, or quality of life in patients with AF without systolic impairment, and generally consistent with the overall lack of effect in patients with heart failure and preserved ejection fraction found in the ALDO-DHF (Aldosterone Receptor Blockade in Diastolic Heart Failure)[26] and TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist)[27] trials. Of interest, in the ALDO-DHF trial of predominantly hypertension-related heart failure and preserved ejection fraction aldosterone inhibition reduced E/e' but did not increase in VO_{2peak}, and in another trial spironolactone improved VO_{2peak} and reduced exercise-induced increase in E/e' in a selected population of patients with heart failure and preserved ejection fraction that excluded patients with AF.[26,28] Of note, although the TOPCAT trial showed overall neutral results this may be confounded by the quality issues in Eastern Europe.[29] In the IMPRESS-AF trial, the hospitalization rates were numerically higher in the placebo arm. A larger study that is powered for hospitalizations and cardiovascular death might produce other results, although such a study would be difficult to justify based on the overall results of spironolactone trials in patients with preserved ejection fraction.

Although patients receiving spironolactone had numerically more cases of spontaneous return to sinus rhythm such cases were few in both study arms, the

Table 3. Subgroup Analysis of the Primary Outcome

Analyses	Spironolactone		Placebo		Treatment Effect (95% CI)*	Estimate of Difference (95% CI)*,†	*P* Value for Interaction*
	Mean (SD)	n	Mean (SD)	n			
Pre-specified subgroup analyses							
Peak VO_2, mL/min per kg							
VO_2 ≤16	11.2 (4.4)	60	11.9 (3.7)	63	−0.56 (−1.85 to 0.73)	0.64 (−1.38 to 2.66)	0.54
VO_2 >16	18.1 (3.9)	43	18.2 (4.6)	43	0.07 (−1.47 to 1.62)		
Age, y							
Age ≤ median‡	14.4 (6.3)	54	16.6 (4.8)	53	−1.40 (−2.76 to −0.05)	2.24 (0.28 to 4.20)	0.03
Age > median	13.7 (4.3)	49	12.3 (4.6)	53	0.83 (−0.55 to 2.22)		
BMI, kg/m^2							
BMI <25	14.7 (3.9)	14	15.2 (4.9)	14	0.30 (−2.40 to 2.99)	…	0.13
25 to <30	14.9 (6.5)	43	16.4 (5.0)	36	−1.59 (−3.21 to 0.02)	−1.89 (−5.05 to 1.27)	
BMI ≥30	13.0 (4.5)	46	13.0 (5.0)	55	0.58 (−0.85 to 2.00)	0.28 (−2.79 to 3.35)	
Sex							
Women	11.0 (3.7)	20	12.1 (2.9)	26	−0.41 (−2.54 to 1.72)	0.14 (−2.28 to 2.57)	0.91
Men	14.8 (5.5)	83	15.2 (5.5)	80	−0.27 (−1.39 to 0.86)		
Systolic blood pressure, mm Hg							
SBP ≤ median‡	13.5 (6.2)	52	14.8 (5.2)	54	−0.71 (−2.10 to 0.68)	0.93 (−1.06 to 2.93)	0.36
SBP > median	14.6 (4.4)	51	14.0 (5.1)	51	0.23 (−1.19 to 1.64)		
Diastolic blood pressure, mm Hg							
DBP ≤ median‡	13.5 (5.6)	54	13.7 (5.2)	58	−0.24 (−1.58 to 1.11)	−0.09 (−2.08 to 1.90)	0.93
DBP > median	14.7 (5.1)	49	15.3 (5.0)	47	−0.33 (−1.78 to 1.12)		
Post-hoc subgroup analysis							
E/E’							
E/E’ <10	15.3 (5.2)	56	15.1 (5.1)	58	−0.26 (−1.60 to 1.10)	…	0.73
10 <14	13.0 (4.9)	34	13.9 (5.5)	30	0.06 (−1.75 to 1.85)	0.31 (−1.95 to 2.58)	
E/E’ ≥14	11.2 (6.2)	13	13.4 (4.8)	18	−1.23 (−3.86 to 1.40)	−0.97 (−3.93 to 1.99)	

BMI indicates body mass index; DBP, diastolic blood pressure; and SBP, systolic blood pressure; and $VO_{2peak,}$ peak oxygen consumption; mean is unadjusted.

*The mean differences between the spironolactone group and the placebo group, 95% CIs, and the corresponding *P* values were estimated from linear regression models adjusting for the baseline continuous peak oxygen consumption score.

†The lower level was always treated as the reference group for the estimates of treatment difference apart from sex for which women were the reference group.

‡The median age is 72.58 years, median systolic blood pressure is 129 mm Hg, and median diastolic blood pressure is 74 mm Hg (placebo group is the reference group).

difference was not significant statistically, and could therefore be a chance finding. The recently published RACE-3 trial suggested that a complex intervention including spironolactone was associated with a higher rate of sinus rhythm maintenance at 1 year (*P*=0.042).[11] The RACE-3 intervention consisted of mineralocorticoid receptor antagonists, statins, angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers, and cardiac rehabilitation.[11] Among the targeted trial medicines, the mineralocorticoid receptor antagonists showed the most prominent contrast in use (85% in the treatment group and 4% in the control group). Whilst the RACE-3 trial indicated the mineralocorticoid receptor antagonists could help maintenance of the sinus rhythm in the recent onset AF, spontaneous return in sinus rhythm was infrequent in both arms of the IMPRESS-AF trial. The actual baseline VO_{2peak} of 14.25 mL/kg per minute was lower than the projected 16 mL/kg per minute, possibly reflecting the background chronic AF, but this is unlikely to affect the study conclusions.

Overall, spironolactone was well tolerated. There were comparable rates of withdrawal from the study in the treatment and control groups. As expected, spironolactone reduced BP, thus demonstrating adequate overall compliance with the drug as confirmed by the expected effect. However, we found a safety signal as there was a reduction of 6.0 mL/kg in the estimated glomerular filtration rate over 2 years. These data indicate potential harm to the kidney caused by treating patients with AF with spironolactone. However, most patients with pharmacological inhibition of renin-angiotensin-aldosterone system, including spironolactone have hemodynamically

Table 4. Secondary Outcomes: Return to Sinus Rhythm and Hospitalization for All Causes

Analyses at 2 y	Spironolactone		Placebo		Odds Ratio (95% CI)	*P* Value
Sinus rhythm, n (%)*	n=101	8 (8%)	n=106	4 (4%)	2.19 (0.64–7.52)†	0.21†
Hospitalization for all causes						
Participants with at least 1 event, n (%)	n=118	18 (15%)‡	n=123	28 (23%)	0.65 (0.36–1.17)§	0.15§
Incidence rate (no. per 10 000 person-days)	n=118	2.46	n=123	3.78		

*Spontaneous return to sinus rhythm on ECG.
†The odds ratios, 95% CIs, and the corresponding *P* values were estimated from a logistic regression model, after adjustment for the continuous baseline peak oxygen consumption.
‡One first hospitalized event had no date and was excluded from the time-to-event analysis.
§The adjusted hazard ratio, 95% CIs, and the corresponding *P* values were estimated from a Cox regression model adjusting for the baseline continuous peak oxygen consumption score for the primary analysis (placebo group is the reference group).

mediated reductions in glomerular filtration rates.[30] These changes can be renal protective by decreasing chronic glomerular hyperfiltration in patients with chronic kidney disease and they may have contributed the decrease in HF hospitalization that was observed in the TOPCAT trial. Not unexpectedly, a higher occurrence of breast pain/swelling and hyperkalemia was noted in the spironolactone group.

Limitations

The study outcomes were assessed by tests of physical capacity, but these tests could be inherently affected by various musculoskeletal problems despite every effort to perform the tests until the limits of the cardiac reserve are reached. Although recognized questionnaires were used to assess quality of life, specific validation of the tests in the study population has not been done.

There was a relatively high drop-out rate in this study, and overall 16% of patients did not complete the primary outcome tests. However, the study power was estimated to allow 20% loss of the patients during follow-up, and the validity of the findings was maintained. The study did not have power to reliably define effects of spironolactone on hard outcomes, such as hospitalizations or return to sinus rhythm. However, given the detrimental effects of the drug on kidney function in this trial population further testing of spironolactone will need careful consideration.

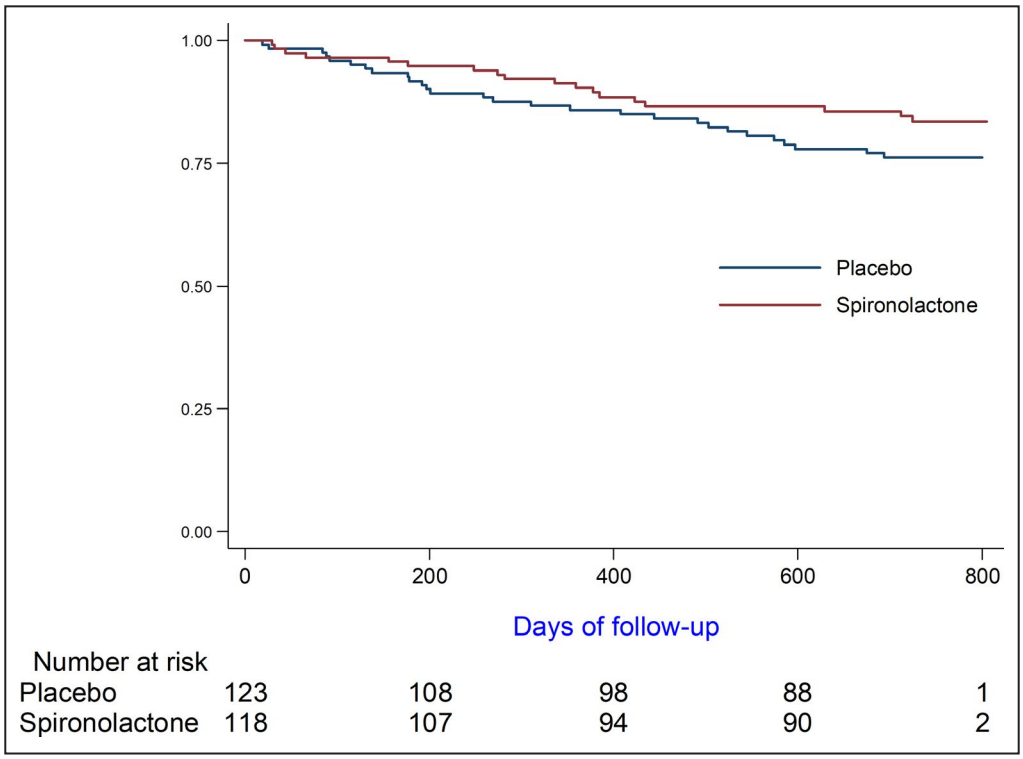

Figure 2. Kaplan–Meier plot of time to first hospitalization.

CONCLUSIONS

Treatment with the aldosterone antagonist, spironolactone in patients with permanent AF and preserved ejection fraction does not improve exercise tolerance, quality of life, and diastolic function. Furthermore, spironolactone leads to worsening of renal function which should be considered in this patient population and use of mineralocorticoid receptor antagonists may mandate closer monitoring of renal function.

ARTICLE INFORMATION

Received March 4, 2020; accepted June 29, 2020.

Affiliations

From the North Worcestershire VTS, St Helens and Knowsley Teaching Hospitals NHS Trust, Prescot, Merseyside, United Kingdom (E.S.); Institute of Cardiovascular Sciences (E.S., F.S., P.K.), Birmingham Clinical Trials Unit, Institute of Applied Health Research (Y.S., J.D.), NIHR Birmingham Biomedical Research Centre (J.D., M.C.) and Centre for Patient Reported Outcomes Research (CPROR), Institute of Applied Health Research (M.C.), University of Birmingham, United Kingdom; National Institute for Health Research (NIHR) Applied Research Centre West Midlands, University of Birmingham, United Kingdom (M.C.); National Institute for Health Research Surgical Reconstruction and Microbiology Research Centre, University of Birmingham, United Kingdom (M.C.); Birmingham Health Partners Centre for Regulatory Science and Innovation, University of Birmingham, United Kingdom (M.C.); Department of Physiology, Faculty of Medical and Health Sciences, University of Auckland, New Zealand (J.P.F.); University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom (P.K.); Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, United Kingdom (P.K.); University Heart and Vascular Center, UKE Hamburg, Hamburg, Germany (P.K.); German Center for Cardiovascular Research (DZHK), partner site Hamburg/Kiel/Lübeck, Hamburg, Germany (P.K.); Academic Unit of Primary Care, Warwick Medical School, University of Warwick, Coventry, United Kingdom (P.S.G.); Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom (G.Y.L.); and Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark (G.Y.L.).

Acknowledgments

Author contributions: Dr Shantsila wrote the first draft of the report. Dr Sun and Prof Deeks performed statistical analysis and edited the article. Dr Shahid, Prof Gill, Prof Fisher, Prof Kirchhof, and Prof Lip edited the article.

Sources of Funding

The trial was funded by the NIHR, NIHR-EME Programme (grant number 12/10/19) with support from NIHR Clinical Research Network West Midlands, United Kingdom. The University of Birmingham was the sponsor of this trial.

Disclosures

Prof Lip reports acting as a Consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon, and Daiichi-Sankyo; Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees were directly received personally. Prof Calvert reports grants from NIHR HTA, during the conduct of the study; grants from NIHR Birmingham Biomedical Research Centre, grants from NIHR Surgical Reconstruction and Microbiology Research Centre, grants from Health Data Research UK, grants from Innovate UK, grants from Macmillan Cancer Support, personal fees from PCORI, from Astellas, from Takeda, from Glaukos, from Merck, outside the submitted work. Prof Fisher reports grants from NIHR, during the conduct of the study; grants from BMS/Pfizer, outside the submitted work. Prof Kirchhof is a board member of the European Society of Cardiology and has received travel support from the European Society of Cardiology, including for meetings pertinent to this work, during the conduct of the study; Prof Kirchhof has received research support from European Union, British Heart Foundation, Leducq Foundation, Medical Research Council (UK), and German Centre for Heart Research, from several drug and device companies active in atrial fibrillation, and has received honoraria from several such companies, outside the submitted work; In addition, Prof Kirchhof is listed as an inventor on 2 patents held by University of Birmingham (Atrial Fibrillation Therapy WO 2015140571, Markers for Atrial Fibrillation WO 2016012783), pending. The remaining authors have no disclosures to report.

Supplementary Materials

Data S1
Tables S1–S8
References 31–35

REFERENCES

1. Santhanakrishnan R, Wang N, Larson MG, Magnani JW, McManus DD, Lubitz SA, Ellinor PT, Cheng S, Vasan RS, Lee DS, et al. Atrial fibrillation begets heart failure and vice versa: temporal associations and differences in preserved versus reduced ejection fraction. *Circulation*. 2016;133:484–492.
2. Corley SD, Epstein AE, DiMarco JP, Domanski MJ, Geller N, Greene HL, Josephson RA, Kellen JC, Klein RC, Krahn AD, et al. Relationships between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study. *Circulation*. 2004;109:1509–1513.
3. Dzeshka MS, Lip GY, Snezhitskiy V, Shantsila E. Cardiac fibrosis in patients with atrial fibrillation: mechanisms and clinical implications. *J Am Coll Cardiol*. 2015;66:943–959.
4. Normand C, Kaye DM, Povsic TJ, Dickstein K. Beyond pharmacological treatment: an insight into therapies that target specific aspects of heart failure pathophysiology. *Lancet*. 2019;393:1045–1055.
5. Chua W, Purmah Y, Cardoso VR, Gkoutos GV, Tull SP, Neculau G, Thomas MR, Kotecha D, Lip GYH, Kirchhof P, et al. Data-driven discovery and validation of circulating blood-based biomarkers associated with prevalent atrial fibrillation. *Eur Heart J*. 2019;40:1268–1276.
6. Weber KT. Aldosterone in congestive heart failure. *N Engl J Med*. 2001;345:1689–1697.
7. Burniston JG, Saini A, Tan LB, Goldspink DF. Aldosterone induces myocyte apoptosis in the heart and skeletal muscles of rats in vivo. *J Mol Cell Cardiol*. 2005;39:395–399.
8. Brilla CG, Zhou G, Matsubara L, Weber KT. Collagen metabolism in cultured adult rat cardiac fibroblasts: response to angiotensin II and aldosterone. *J Mol Cell Cardiol*. 1994;26:809–820.
9. Tsai CT, Chiang FT, Tseng CD, Hwang JJ, Kuo KT, Wu CK, Yu CC, Wang YC, Lai LP, Lin JL. Increased expression of mineralocorticoid receptor in human atrial fibrillation and a cellular model of atrial fibrillation. *J Am Coll Cardiol*. 2010;55:758–770.
10. Zannad F, Alla F, Dousset B, Perez A, Pitt B. Limitation of excessive extracellular matrix turnover may contribute to survival benefit of spironolactone therapy in patients with congestive heart failure: insights from the randomized aldactone evaluation study (RALES). Rales Investigators. *Circulation*. 2000;102:2700–2706.
11. Rienstra M, Hobbelt AH, Alings M, Tijssen JGP, Smit MD, Brugemann J, Geelhoed B, Tieleman RG, Hillege HL, Tukkie R, et al. Targeted therapy of underlying conditions improves sinus rhythm maintenance in patients with persistent atrial fibrillation: results of the RACE 3 trial. *Eur Heart J*. 2018;39:2987–2996.
12. Calvert M, Kyte D, von Hildebrand M, King M, Moher D. Putting patients at the heart of health-care research. *Lancet*. 2015;385:1073–1074.
13. Shantsila E, Haynes R, Calvert M, Fisher J, Kirchhof P, Gill PS, Lip GY. IMproved exercise tolerance in patients with PReserved Ejection fraction by Spironolactone on myocardial fibrosiS in Atrial Fibrillation rationale and design of the IMPRESS-AF randomised controlled trial. *BMJ Open*. 2016;6:e012241.
14. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P; Guidelines ESCCfP. 2012 focused update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J*. 2012;33:2719–2747.

15. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37:2893–2962.
16. Rector TS, Kubo SH, Cohn JN. Validity of the Minnesota Living with Heart Failure questionnaire as a measure of therapeutic response to enalapril or placebo. *Am J Cardiol*. 1993;71:1106–1107.
17. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med*. 2001;33:337–343.
18. Guazzi M, Arena R, Halle M, Piepoli MF, Myers J, Lavie CJ. 2016 focused update: clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *Eur Heart J*. 2018;39:1144–1161.
19. Scott JM, Haykowsky MJ, Eggebeen J, Morgan TM, Brubaker PH, Kitzman DW. Reliability of peak exercise testing in patients with heart failure with preserved ejection fraction. *Am J Cardiol*. 2012;110:1809–1813.
20. Nagueh SF, Kopelen HA, Quinones MA. Assessment of left ventricular filling pressures by Doppler in the presence of atrial fibrillation. *Circulation*. 1996;94:2138–2145.
21. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA, Evangelisa A. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *Eur J Echocardiogr*. 2009;10:165–193.
22. Calvert M, Blazeby J, Altman DG, Revicki DA, Moher D, Brundage MD; Group CP. Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension. *JAMA*. 2013;309:814–822.
23. Cicoira M, Zanolla L, Rossi A, Golia G, Franceschini L, Brighetti G, Marino P, Zardini P. Long-term, dose-dependent effects of spironolactone on left ventricular function and exercise tolerance in patients with chronic heart failure. *J Am Coll Cardiol*. 2002;40:304–310.
24. Obokata M, Olson TP, Reddy YNV, Melenovsky V, Kane GC, Borlaug BA. Haemodynamics, dyspnoea, and pulmonary reserve in heart failure with preserved ejection fraction. *Eur Heart J*. 2018;39:2810–2821.
25. Reddy YNV, Olson TP, Obokata M, Melenovsky V, Borlaug BA. Hemodynamic correlates and diagnostic role of cardiopulmonary exercise testing in heart failure with preserved ejection fraction. *JACC Heart Fail*. 2018;6:665–675.
26. Edelmann F, Wachter R, Schmidt AG, Kraigher-Krainer E, Colantonio C, Kamke W, Duvinage A, Stahrenberg R, Durstewitz K, Loffler M, 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;309:781–791.
27. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med*. 2014;370:1383–1392.
28. Kosmala W, Rojek A, Przewlocka-Kosmala M, Wright L, Mysiak A, Marwick TH. Effect of aldosterone antagonism on exercise tolerance in heart failure with preserved ejection fraction. *J Am Coll Cardiol*. 2016;68:1823–1834.
29. Pfeffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, et al. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. *Circulation*. 2015;131:34–42.
30. Bianchi S, Bigazzi R, Campese VM. Long-term effects of spironolactone on proteinuria and kidney function in patients with chronic kidney disease. *Kidney Int*. 2006;70:2116–2123.
31. Little RJA. Missing-data adjustments in large surveys. *J Bus Econ Stat*. 1988;6:287–296.
32. Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. New York, Chichester, Brisbane, Toronto, Singapore: Wiley; 1987.
33. Shafiq A, Brawner CA, Aldred HA, Lewis B, Williams CT, Tita C, Schairer JR, Ehrman JK, Velez M, Selektor Y, et al. Prognostic value of cardiopulmonary exercise testing in heart failure with preserved ejection fraction. The Henry Ford HospITal CardioPulmonary EXercise Testing (FIT-CPX) project. *Am Heart J*. 2016;174:167–172.
34. Swank AM, Horton J, Fleg JL, Fonarow GC, Keteyian S, Goldberg L, Wolfel G, Handberg EM, Bensimhon D, Illiou MC, et al. Modest increase in peak VO_2 is related to better clinical outcomes in chronic heart failure patients: results from heart failure and a controlled trial to investigate outcomes of exercise training. *Circ Heart Fail*. 2012;5:579–585.
35. Edelmann F, Gelbrich G, Dungen HD, Frohling S, Wachter R, Stahrenberg R, Binder L, Topper A, Lashki DJ, Schwarz S, et al. Exercise training improves exercise capacity and diastolic function in patients with heart failure with preserved ejection fraction: results of the Ex-DHF (Exercise training in Diastolic Heart Failure) pilot study. *J Am Coll Cardiol*. 2011;58:1780–1791.

SUPPLEMENTAL MATERIAL

Data S1.

The primary analysis followed modified intention to treat principles including participants regardless of their compliance with the medication. Participants with missing data for the final assessment were excluded except for those who died before the two-year follow-up assessment. For these participants, their peak VO_2 scores at two years were imputed as zero values regardless of cause. Whilst the value of zero was not actually measured, it allowed inclusion of the patient in the study and it should be a suitable reflection of the health state of the patient.

The following sensitivity analyses were undertaken:

a) Per-protocol analysis: participants with ≥80% allocated capsules taken with a final follow-up assessment for peak VO_2 (with zero imputed if they died as in the intention-to-treat analysis). Participants for whom compliance data could not be obtained were excluded from the per protocol analysis;
b) Complete case analysis: participants who completed the two-year follow-up assessment;
c) Multiple imputation: outcomes for participants within missing two-year follow-up assessment who had not died were imputed using a multivariate imputation approach, which filled in missing values in multiple variables iteratively by using chained equations that assumed an arbitrary missing data pattern. The Predictive Mean Matching (PMM)[31] method was implemented which produces imputed values that better match the observed values than linear regression models, especially when peak VO_2 score were not normally distributed. Missing data for participants in the spironolactone group and the placebo group were imputed separately, which would allow unbiased estimates for any interaction effects between the treatment and any covariate in the analysis model. Baseline peak VO_2, age, BMI, systolic and diastolic blood pressure, six minute walk test distance, BNP level, E/E' ratio, EQ-5D-5L, MLWHF scores and sex were included in the imputation model and used to generate 20 simulated data-sets. Analyses were then performed on each set with the results combined using Rubin's rules[32] to obtain a single set of results.

For all the above outcomes, secondary analyses had been repeated by including additional adjustments for age, sex and BMI at baseline.

Analyses of secondary outcomes were performed on the modified intention to treat basis as for the primary outcome. For the six minute walk test, the analysis substituted a zero value for

those participants who had died before the two-year follow-up assessment regardless of causes. For EQ-5D-5L and Minnesota Living with Heart Failure questionnaire (MLWHF) at one year and two years, scores indicating the worst level of quality of life observed across the whole dataset were substituted for those who had died before the one-year and two-year follow-up assessment, respectively, regardless of causes, where a higher score reflecting poorer quality of life for MLWHF and better quality of life for EQ-5D-5L. For the MLWHF, if up to four of the 21 responses were missing mean substitution was used to impute the missing responses and compute the overall score; otherwise, the score was coded as missing. Analyses for the remaining secondary outcomes had been undertaken on complete cases only.

The primary outcome analysis was undertaken using multiple linear regression including the baseline continuous continuous peak VO_2 score and treatment group as covariates. Multiple linear regression was also used for the following continuous outcomes, adjusting for the corresponding baseline value of each outcome in addition to the baseline continuous peak VO_2 score (accounting the stratifying variable used in the randomization):

- Exercise tolerance measured by six minute walk test walk test at two years
- Quality of life measured by MLWHF and EQ-5D-5L at one and two years
- Left ventricular diastolic function measured by E/E' at two years
- Brain natriuretic peptide level at two years

In all cases the treatment effect estimate was a difference in mean values (spironolactone – placebo) with the uncertainty in the estimate expressed using a 95% confidence interval.

The following pre-defined subgroups at baseline were compared for the primary outcome peak VO_2 by inclusion of an interaction term (treatment by subgroup) in the linear regression model in addition to their main effects and baseline continuous peak VO_2 score.

- Peak VO_2 categories (mL/min/kg): <=16 vs >16
- Sex: male vs female
- Age groups (years): split at median
- BMI groups (kg/m^2): <25 (normal or underweight), 25 to <30 (overweight), and ≥30 (obesity)
- Systolic blood pressure groups (mmHg): split at median
- Diastolic blood pressure groups (mmHg): split at median

Multiple logistic regression was carried out analysis of the spontaneous return to sinus rhythm on electrocardiogram at two years, adjusting only for baseline continuous peak VO_2 score. An additional analysis was undertaken additionally adjusting for the log transformed BNP levels at baseline as this is known to be predictive of this outcome. The treatment effect estimate was an odds ratio (odds on spironolactone compared to placebo) with the uncertainty expressed using a 95% confidence interval.

Cox regression model was used to analyse the time to hospitalisation event data (for any cause) over two years, adjusted for baseline continuous peak VO_2 score. Data on participants who had not been hospitalised over the two-year period were censored at the date of their last visit attended for clinical events, those who died who or were lost to follow-up were censored on their last visit date if they had not been hospitalised. A Kaplan-Meier plot of time to the first hospitalisation of any cause was presented. The treatment effect estimate was a hazard ratio (hazard on spironolactone compared to placebo) with the uncertainty expressed using a 95% confidence interval.

Major adverse clinical events, as listed below:

- Death from all causes
- Death from cardiac causes
- Hospitalisation for cardiac causes
- Stroke
- Systemic thromboembolism

were compared between the two treatment groups using Fisher's exact test.

Absolute changes in creatinine, estimated glomerular filtration rate, systolic blood pressure and diastolic blood pressure from baseline to two years were computed within each arm, and compared as a difference in mean change between arms (with statistical significance assessed using a t test)

The following known safety issues with the intervention drug were assessed at each visit and reported by treatment arms: Formal comparisons had not been undertaken.

- Estimated glomerular filtration <30 mL/min/1·73m^2
- Hyperkalaemia (≥5·1 mmol/L)

- Hyperkalaemia (≥6·0 mmol/L)
- Creatinine >220 μmol/L
- Breast pain
- Breast swelling
- Allergic reaction to the trial medication

In addition, the spontaneously reported adverse events were classified by the principle investigator and chief investigator, and tabulated by treatment group.

Stata version 12 software was used for all analyses.

Sample size

Sample size was determined to be able to show a clinically important difference in the primary outcome of peak VO_2.Published values of peak VO_2 in subjects with HF give baseline values (mean 16 [SD 5] mL/min/kg)[23] and data in HFpEF suggest that a difference of two mL/min/kg would be clinically relevant, and was used for the design of the recent Aldo-DHF study of spironolactone in patients with HFpEF, 95% of whom were free from AF.[26, 33, 34] Unfortunately, the study by Cicoira et al,[23] used for power calculation does not give a standard deviation of in peak VO_2 but a similar trial, Edelmann et al[35] provides that statistic (five mL/min/kg) and also reports a similar magnitude of the effect. A sample size of 100 participants in each arm would give the power of at least 80% to detect differences in primary and secondary endpoints of a magnitude consistent with published results from similar studies. We increased the sample size to 125 per arm for provision for a 20% drop out rate. Statistical power would be higher should this rate be too pessimistic, and with the benefits of adjusting for baseline values.

Table S1. Timeline of trial procedures and follow up schedule.

			Follow-up								
Visit	Screening	Baseline	Month 1	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24
		Additional visits were arranged to reassess potassium levels if patient's blood results show a potassium level of >5·0 mmol/L									
Eligibility Check	X	X									
Informed consent	X										
Relevant medical history taken	X										
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X
Standard clinical examination including BP check	X	X	X	X	X	X	X	X	X	X	X
Clinical Biochemistry											
Full blood count	X		X	X	X	X	X	X	X	X	X
Renal function, potassium, sodium	X		X	X	X	X	X	X	X	X	X
HBA1c (for diabetics)	X										
Lipid levels	X										
Electrocardiogram	X										X
Echocardiogram	X										X
Brain Natriuretic Peptide test	X										X
Randomisation		X									
Dispensing of study drug		X			X		X		X		
Cardiopulmonary exercise testing		X									X
Six-minute walk test		X									X

Quality of life questionnaires (MLWHFQ and EQ-5D)		X					X				X

Table S2. Changes in clinical characteristics.

Changes in clinical characteristics	Spironolactone		Placebo		Mean difference (95% CI)[1]	P-value*
	mean (SD)	n (%)	mean (SD)	n (%)		
Exploratory outcomes (changes in clinical characteristics)						
Serum creatinine						
Baseline	90 (23)	125 (100%)	90 (20)	125 (100%)		
24 months	99 (23)	101 (81%)	92 (21)	106 (85%)		
Change from baseline to 24 months	8.9 (13.8)	101 (81%)	2.0 (12.1)	106 (85%)	6.9 (3.4 to 10.5)	0.0002
Estimated glomerular filtration rate						
Baseline	70 (16)	125 (100%)	69 (17)	125 (100%)		
24 months	64 (15)	101 (81%)	69 (14)	106 (85%)		
Change from baseline to 24 months	-6.8 (11.3)	101 (81%)	-0.8 (12.3)	106 (85%)	-6.0 (-9.3 to -2.8)	0.0003
Systolic blood pressure						
Baseline	129 (16)	125 (100%)	130 (15)	124 (99%)		
24 months	123 (18)	101 (81%)	130 (16)	106 (85%)		
Change from baseline to 24 months	-6.7 (19.8)	101 (81%)	0.6 (17.0)	105 (84%)	-7.2 (-12.3 to -2.2)	0.005

Diastolic blood pressure						
Baseline	76 (11)	125 (100%)	76 (14)	124 (99%)		
24 months	72 (11)	101 (81%)	74 (12)	106 (85%)		
Change from baseline to 24 months	-3.9 (12.2)	101 (81%)	-1.3 (14.4)	105 (84%)	-2.6 (-6.3 to 1.1)	0.17

*The mean differences between spironolactone and placebo groups, 95% confidence intervals (CIs) and the corresponding p values were obtained using two sample t test (placebo group is the reference group)

SD: standard deviation

Table S3. Study outcomes additionally adjusted for age, sex and BMI.

Analyses of VO_{2peak} at 2 years	Spironolactone		Placebo		Treatment effect	p-value*
	Mean (SD)	n	Mean (SD)	n	(95% CI)*	
Primary outcome†						
VO_{2peak} (mL/kg/min)	14.0 (5.38)	103	14.5 (5.16)	105	-0.32 (-1.32 to 0.68)	0.53
Primary outcome sensitivity analysis						
Per protocol analysis:‡ VO_{2peak} (mL/kg/min)	14.8 (4.32)	57	14.9 (4.92)	76	0.17 (-0.81 to 1.14)	0.73
Complete case analysis: VO_{2peak} (mL/kg/min)	14.8 (4.45)	98	14.9 (4.59)	102	-0.14 (-0.89 to 0.61)	0.71
Multiple imputation method:§ VO_{2peak} (mL/kg/min)	13.4 (6.04)[5]	125	14.0 (5.48)‖	125	-0.53 (-1.57 to 0.51)	0.31
Secondary outcomes						
Six-minute walk test distance (m)#	313 (108)	105	331 (112)	106	-8.30 (-31.9 to 15.3)	0.49
E/E′ ratio	9.00 (3.05)	101	9.69 (3.57)	105	-0.64 (-1.48 to 0.20)	0.13
Brain natriuretic peptide (pg/mL)	179 (171)	101	187 (109)	104	4.37 (-28.5 to 37.3)	0.79
EQ-5D-5L score	0.81 (0.26)	98	0.84 (0.21)	103	-0.004 (-0.05 to 0.04)	0.86
MLWHF score**	17.4 (22.7)	96	15.3 (20.4)	103	0.27 (-4.60 to 5.14)	0.91

VO_{2peak}: peak oxygen consumption; SD: standard deviation

*The mean differences between spironolactone group and placebo group, 95% confidence intervals (CIs) and the corresponding p values were estimated from linear regression models adjusting for the baseline continuous VO_{2peak} score. In the sensitivity analyses additional adjustments for age, sex and BMI were made.

†A value of 0 was assigned to VO_{2peak} score for those who died before the 2-year follow-up assessment

‡Per-protocol population was defined as ≥80% of capsules taken across the full 2-year trial duration or up to the time of death

§Predictive Mean Matching (PMM) imputation method was used to generate 20 imputed data-sets. Data for participants in spironolactone group and placebo group were imputed separately. $VO_{2peak,}$ age, BMI, systolic/diastolic blood pressure, six-minute walk test, BNP level, E/E' ratio, EQ-5D-5L, MLWHF scores at baseline and sex were included in the imputation model.

‖Estimates of the standard deviation have been obtained by multiplying the standard error by the square root of 125

#For 6-minute walk test, a value of 0 was assigned to those who died; for EQ-5D-5L score, a value of 0 was assigned to those who died; for MLWHF questionnaire, the highest value across the whole participants was assigned to those who died

**Minnesota Living with Heart Failure (MLWHF) questionnaire; score ranges from 0 to 105 with a higher score reflecting poorer quality of life. All patients choose to use the English version of the questionnaires with only one proxy completion case recorded for completion of the questionnaires.

(Placebo group is the reference group)

Table S4. Quality of life scores at one year.

Analyses	Spironolactone		Placebo		Treatment effect (95% CI)*	p-value*
	Mean (SD)	n	Mean (SD)	n		
Primary analysis						
EQ-5D-5L score	0.82 (0.22)	106	0.84 (0.19)	111	-0.01 (-0.05 to 0.03)	0.63
MLWHF score†	18.4 (20.9)	101	16.9 (17.8)	110	1.24 (-2.48 to 4.96)	0.51
Secondary analysis (additionally adjusted for age, sex and BMI)						
EQ-5D-5L score	0.82 (0.22)	106	0.85 (0.18)	109	-0.008 (-0.05 to 0.03)	0.72
MLWHF score†	18.4 (20.9)	101	16.3 (17.3)	108	1.35 (-2.40 to 5.10)	0.48

*The mean differences between spironolactone group and placebo group, 95% confidence intervals (CIs) and the corresponding p values were estimated from linear regression models, after adjustment for the baseline continuous VO_{2peak} score and the corresponding baseline score of the outcome measure for the primary analyses or additionally adjusted for age, sex and BMI for the secondary analyses

SD: standard deviation

†Minnesota Living with Heart Failure (MLWHF) questionnaire; score ranges from 0 to 105 with a higher score reflecting poorer quality of life. All patients choose to use the English version of the questionnaires with only one proxy completion case recorded for completion of the questionnaires.

(Placebo group is the reference group)

Table S5. Secondary outcomes: return to sinus rhythm and hospitalization for all causes additionally adjusted for age, sex and BMI.

Analyses	Spironolactone		Placebo		Odds Ratio (95% CI)	p-value
Sinus rhythm, n (%)*	n=101	8 (7.9%)	n=105	4 (3.8%)	2.14 (0.62 to 7.35) †	0.23†
Hospitalization for all causes						
Participants with at least one event, n (%)	n=118	18 (15.3%)‡	n=121	27 (22.3%)	0.62 (0.34 to 1.14)§	0.12§
Incidence rate (no. per 10000 person days)	n=118	2.46	n=121	3.69		

*Spontaneous return to sinus rhythm on electrocardiogram after 2 years of treatment

†The odds ratios, 95% confidence interval (CIs) and the corresponding p values were estimated from a logistic regression model, after adjustment for the continuous VO_{2peak} and BNP level score at baseline for the primary analysis and additionally adjusted for age, sex and BMI for the secondary analysis

‡One first hospitalized event had no date and was excluded from the time to event analysis

§The adjusted hazard ratio, 95% confidence intervals (CIs) and the corresponding p values were estimated from a Cox regression model adjusting for the baseline continuous VO_{2peak} score for the primary analysis and additionally adjusted for age, sex and BMI for the secondary analysis (placebo group is the reference group)

(Placebo group is the reference group)

Table S6. Adverse events and serious adverse events.

AEs/SAEs*	Spironolactone (n=125)	Placebo (n=125)	P-value†
All SAEs			
Total number of patients experiencing at least one SAE, n (%)	23 (18.4%)	32 (25.6%)	
Total number of SAEs	27	42	0.22
Prespecified major adverse clinical events (SAEs)			
	(n=121[3])	(n=123[3])	
Death from all causes, n (%)	5 (4.1%)	3 (2.4%)	0.50
Death from cardiac causes, n (%)	5§ (4.1%)	1 (0.8%)	0.12
Hospitalization for cardiac causes, n (%)	2 (1.7%)	6‖ (4.9%)	0.28
Stroke, n (%)	0 (0.0%)	2 (1.6%)	0.50
Systemic thromboembolism, n (%)	0 (0.0%)	1 (0.8%)	1.00
Prespecified safety outcomes (AEs)			
Number of patients experiencing at least one episode			
Breast pain, n (%)	17 (14%)	5 (4%)	
Breast swelling, n (%)	11 (9%)	4 (3%)	
Allergic reaction, n (%)	2 (2%)	0 (0%)	
Hyperkalaemia (≥5.1 mmol/L), n (%)	46 (37%)	17 (14%)	
Hyperkalaemia (≥6.0 mmol/L), n (%)	3 (2%)	0 (0%)	
Serum creatinine ever >220 µmol/L, n (%)	1 (1%)	0 (0%)	
Estimated glomerular filtration < 30 mL/min/1.73m^2, n (%)	8 (6%)	2 (2%)	
Total number of episodes			
Breast pain	40	9	
Breast swelling	26	10	
Allergic reaction	2	0	
Hyperkalaemia (≥5.1 mmol/L)	72	30	
Hyperkalaemia (≥6.0 mmol/L)	3	0	

Serum creatinine >220 µmol/L	1	0	
Estimated glomerular filtration < 30 mL/min/1.73m^2	8	2	

*All adverse events reported here were collected at follow up visits

†P-values were obtained using Fisher's exact test for major adverse clinical events

‡Six SAEs (occurred to 6 individuals) were missing on their adjudication results; therefore, the corresponding outcomes for major adverse clinical events were missing where 4 participants were in Spironolactone group and 2 in Placebo group. Where applicable, these 6 participants were not included in the Fisher's exact test and the corresponding percentage calculation

§One participant died from cardiac causes but also had one SAE not adjudicated; so only 3 participants were missing in Spironolactone group in this case and the denominator used for the percentage calculation was 122

‖One participant in Placebo group had 2 hospitalizations for cardiac causes; so only one SAE was counted here for this participant

Table S7. Number of hospitalizations per participant by treatment group.

Number of hospitalizations	Spironolactone (n=125)	Placebo (n=125)
None, n (%)	106 (84.8%)	97 (77.6%)
One, n (%)	17 (13.6%)	22 (17.6%)
Two, n (%)	1 (0.8%)	5 (4.0%)
Three, n (%)	1 (0.8%)	0 (0.0%)
Four, n (%)	0 (0.0%)	1 (0.8%)

Table S8. Causes of death in the study patients.

Spironolactone (all deaths – 5	Placebo all deaths – 3
Sudden onset (deceased)	Unresponsive in house, likely to be seizure
Seizure AF	E. coli septicaemia, Multi organ failure
Myocardial infarction	Intracranial bleeding
Died due to complications of Bypass surgery	
Died of clostridium difficile bacterial sepsis	