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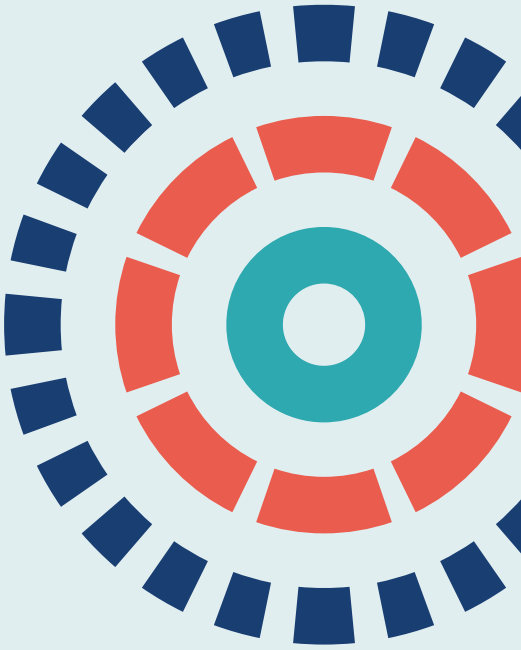

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Spironolactone to improve exercise tolerance in people with permanent atrial fibrillation and preserved ejection fraction: the IMPRESS-AF RCT

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Abstract

Spironolactone to improve exercise tolerance in people with permanent atrial fibrillation and preserved ejection fraction: the IMPRESS-AF RCT

Eduard Shantsila,[1,2,3,4*] Farhan Shahid,[1,2] Yongzhong Sun,[5] Jonathan J Deeks,[5,6] Ronnie Haynes,[2,7] Melanie Calvert,[5,8] James P Fisher,[9] Paulus Kirchhof,[1,2,10] Paramjit S Gill[11] and Gregory YH Lip[4]

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Introduction: Patients with atrial fibrillation frequently suffer from heart failure despite having a normal ejection fraction. There is no proven therapy to improve physical capacity and quality of life in patients with permanent atrial fibrillation with preserved cardiac contractility.

Objective: The IMproved exercise tolerance in heart failure with PReserved Ejection fraction by Spironolactone on myocardial fibrosiS in Atrial Fibrillation (IMPRESS-AF) trial addressed whether or not 2 years of treatment with spironolactone, as compared with placebo, improves exercise tolerance, quality of life and diastolic function in patients with permanent atrial fibrillation and preserved left ventricular ejection fraction.

Design: A randomised, single-centre, double-blind, placebo-controlled trial.

Setting: Two hundred and fifty ambulatory patients [mean age 72.3 years (standard deviation 7.4 years); 23.6% female] with permanent atrial fibrillation and left ventricular ejection fraction $\geq$ 55% [mean 60.5% (standard deviation 5.5%)].

Interventions: Treatment with either 25 mg of spironolactone ($n = 125$) or placebo ($n = 125$) daily.

Main outcome measures: The primary efficacy end point was exercise tolerance at 2 years as measured by peak oxygen consumption (VO_2) on cardiopulmonary exercise testing. Secondary end points were quality of life, the ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (E′) (E/E′; a marker of diastolic dysfunction), all-cause hospital admissions and spontaneous return to sinus rhythm. Treatment effects were estimated by adjusting for baseline values.

Study ethics: The study was approved by the National Research and Ethics Committee West Midlands – Coventry and Warwickshire (reference 14/WM/1211). All patients provided informed written consent.

Results: There was no difference in the peak oxygen consumption at 2 years between the spironolactone group [analysed, $n = 103$; mean VO_2 14.03 ml/minute/kg (standard deviation 5.38 ml/minute/kg)] and the placebo group [analysed, $n = 106$; mean VO_2 14.45 ml/minute/kg (standard deviation 5.14 ml/minute/kg)] (adjusted treatment effect −0.28 ml/minute/kg, 95% confidence interval −1.27 to 0.71 ml/minute/kg; $p = 0.58$). The findings were consistent across all sensitivity analyses. For secondary efficacy end points, there was no significant change in the mean 6-minute walking distance (treatment effect −8.47 m, 95% confidence interval −31.87 to 14.93 m; $p = 0.48$). This also held true for the mean ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (E′) (i.e. E/E′), a measure of left ventricular diastolic function (treatment effect −0.64, 95% confidence interval −1.48 to 0.20; $p = 0.13$). The study treatment was also not associated with a significant treatment effect for quality-of-life scores [$p = 0.67$ for the EuroQol-5 Dimensions, five-level version (EQ-5D-5L), questionnaire and $p = 0.84$ for the Minnesota Living with Heart Failure (MLWHF) questionnaire at 2 years]. The findings remained consistent after adjustment for age, sex and body mass index. Spontaneous return to sinus rhythm on electrocardiography, performed at 2 years, was uncommon in both study groups [4% (standard deviation 3.8%) in the placebo group and 8% (standard deviation 7.9%) in the spironolactone group; $p = 0.21$]. At least one hospitalisation for any reason was required by 15.3% of patients in the spironolactone group and 22.8% in the placebo group ($p = 0.15$; after adjustment for age, sex and body mass index, $p = 0.12$). The estimated glomerular filtration rate was reduced by 6 ml/minute/1.73 m^2 at 2 years in patients allocated to spironolactone (with no reduction in those receiving placebo, resulting in a reduction in the p-value of the difference in the estimated glomerular filtration rate between patients in the spironolactone group and those in the placebo group of < 0.001).

Limitations: This was a relatively small study.

Conclusions: Spironolactone therapy does not improve exercise capacity, cardiac function or quality of life in patients with atrial fibrillation and preserved ejection fraction.

Future work: Further testing of spironolactone in patients with atrial fibrillation and preserved ejection fraction would be difficult to justify.

Trial registration: Current Controlled Trials ISRCTN10259346, European Union Clinical Trials Register 2014-003702-33 and ClinicalTrials.gov NCT02673463.

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List of abbreviations

6MWT	6-minute walk test
AF	atrial fibrillation
ALDO-DHF	ALDOsterone receptor blockade in Diastolic Heart Failure
BCTU	Birmingham Clinical Trials Unit
BMI	body mass index
BNP	B-type natriuretic peptide
CHARM	Candesartan in Heart failure–Assessment of Reduction in Mortality and morbidity programme
CI	chief investigator
CONSORT	Consolidated Standards of Reporting Trials
CPET	cardiopulmonary exercise test
E/E′ ratio	mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (E′) ratio
ECG	electrocardiography
eGFR	estimated glomerular filtration rate
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
IMPRESS-AF	IMproved exercise tolerance in heart failure with PReserved Ejection fraction by Spironolactone on myocardial fibrosiS in Atrial Fibrillation
LVEF	left ventricular ejection fraction
MLWHF	Minnesota Living with Heart Failure
NIHR	National Institute for Health Research
NT-pro-BNP	N-terminal pro-B-type natriuretic peptide
PC-CRTU	Primary Care Clinical Research and Trials Unit
PMM	predictive mean matching
PRO	patient-reported outcome
RALES	Randomised Aldactone Evaluation Study
RC-ICS	Research Clinic in the Institute of Cardiovascular Sciences, City Hospital, Birmingham
SD	standard deviation
SPIRIT	Standard Protocol Items for Randomized Trials
TOPCAT	Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist
VO_2	oxygen consumption

Plain English summary

The heart of a patient with 'heart failure' is unable to supply enough blood to their body. In about half of all heart failure patients, the heart actually contracts reasonably well, but it does not relax properly because it is very stiff and so does not fill sufficiently with blood between heartbeats. This condition is more common in patients who also have atrial fibrillation, an irregular heart rhythm (arrhythmia). Such patients have a poor quality of life and a high risk of death. So there is a clear need to find beneficial therapies for patients with atrial fibrillation.

This clinical trial [entitled IMproved exercise tolerance in heart failure with PReserved Ejection fraction by Spironolactone on myocardial fibrosiS in Atrial Fibrillation (IMPRESS-AF)] tested whether or not giving a drug, spironolactone, to patients with atrial fibrillation increases exercise capacity, improves the heart's ability to relax and improves quality of life. Two hundred and fifty patients with atrial fibrillation were randomly (which means by chance, like by flipping a coin) assigned to take either spironolactone or placebo (sham medication) for 2 years. The main tests during the trial included a measure of exercise capacity (using both a bike test and a walking test) and a heart scan. Patients also completed questionnaires asking them about their quality of life. The trial investigators did not see a difference in the effect of spironolactone and placebo on exercise capacity, heart function or patient-reported quality of life. However, safety concerns about the effect of spironolactone on kidney function were noted.

The trial's findings suggest that treatment with spironolactone in patients with atrial fibrillation and preserved left ventricular function does not improve exercise tolerance or quality of life.

Scientific summary

Background

Patients with heart failure and atrial fibrillation have a poor prognosis. There is a lack of established treatments for heart failure with preserved ejection fraction. Heart failure is common in patients with atrial fibrillation and preserved cardiac contractility. Despite the preservation of left ventricular ejection fraction, patients with heart failure and preserved ejection fraction have poor quality of life and high morbidity and mortality. Mineralocorticoid receptor antagonists, such as spironolactone, improve cardiac function and exercise tolerance (and mortality) in patients with heart failure with reduced left ventricular ejection fraction. Atrial fibrillation represents a separate, clinically and numerically significant, phenotype of heart failure with preserved ejection fraction.

Aldosterone is implicated in cardiac collagen deposition and left ventricular fibrosis. Mechanisms of aldosterone-related cardiac fibrosis include myocardial inflammation, oxidative stress and direct stimulation of cardiac fibroblasts to produce collagen. Cardiac expression of mineralocorticoid receptors is increased in atrial fibrillation, thus augmenting the genomic effects of aldosterone. However, the current evidence on the clinical effectiveness of spironolactone in patients with atrial fibrillation with preserved left ventricular ejection fraction on morbidity and quality of life is sparse.

Objectives

The IMproved exercise tolerance in heart failure with PReserved Ejection fraction by Spironolactone on myocardial fibrosiS in Atrial Fibrillation (IMPRESS-AF) trial aimed to evaluate the effect of mineralocorticoid receptor inhibition with spironolactone in participants with permanent atrial fibrillation with preserved left ventricular ejection fraction compared with placebo.

Methods

Design and setting

The IMPRESS-AF trial is a double-blinded, randomised, placebo-controlled single-centre trial conducted in Birmingham, UK. The trial aimed to randomise 250 participants with permanent atrial fibrillation and preserved left ventricular function 1 : 1 to either spironolactone or placebo.

Participants

Eligible patients were male or female and aged $\geq$ 50 years. Permanent atrial fibrillation was defined by the European Society of Cardiology's criteria. All participants had a left ventricular ejection fraction $\geq$ 55% at recruitment, as established by echocardiography during screening. The participants had to be able to perform cardiopulmonary exercise testing using a cycling ergometer and to complete quality-of-life questionnaires.

Inclusion criteria

Inclusion criteria included:

- permanent atrial fibrillation
- age $\geq$ 50 years
- ability to understand and complete questionnaires (with or without use of an interpreter/ translated materials).

Exclusion criteria

Exclusion criteria included:

- left ventricular ejection fraction < 55% (as determined by echocardiography)
- severe systemic illness (with a life expectancy < 2 years)
- severe chronic obstructive pulmonary disease (e.g. requiring home oxygen or chronic oral steroid therapy)
- severe mitral/aortal valve stenosis/regurgitation
- significant renal dysfunction (i.e. serum creatinine levels ≥ 220 µmol/l), anuria, active renal insufficiency, rapidly progressing or severe impairment of renal function, confirmed or were diabetic and had suspected renal insufficiency/diabetic nephropathy
- an increase in potassium levels to > 5 mmol/l
- recent coronary artery bypass graft surgery (i.e. within 3 months)
- use of an aldosterone antagonist within 14 days before randomisation
- used a potassium-sparing diuretic within 14 days before randomisation
- systolic blood pressure > 160 mmHg
- Addison's disease
- hypersensitivity to spironolactone or any of the ingredients in the product
- any characteristic that may interfere with adherence to the trial protocol.

Randomisation

Randomisation was performed after baseline assessments were completed using a secure web-based randomisation system to ensure concealment of allocation. Participants were randomised 1:1, stratified by their baseline peak oxygen consumption (peak VO_2; two stratification groups: participants with a peak $VO_2 \leq 16$ ml/minute/kg and participants with a peak $VO_2 > 16$ ml/minute/kg). The system allocated a unique investigational medicinal product number to each participant.

Intervention

Patients were treated daily with either 25 mg of spironolactone or placebo. Blinding was achieved by overencapsulating the spironolactone and manufacturing a matching placebo. Spironolactone and placebo were packaged into identical containers that were labelled with a unique investigational medicinal product number (Catalent Pharma Solutions, Bathgate, UK).

Follow-up

The participants underwent routine safety follow-up assessements at months 1 and 3 and 3-monthly thereafter. The study's primary and secondary outcomes were collected at month 24. In addition, the quality-of-life questionnaires were completed after 12 months of study treatment.

Main outcome measures

The *primary* efficacy end point was the change in exercise tolerance at 2 years. This was assessed by the difference between the trial arms in peak VO_2 on cardiopulmonary exercise testing at 24 months, adjusted for the baseline values.

The *secondary* efficacy end points were changes in quality of life and diastolic function, and also all-cause hospital admissions and spontaneous return to sinus rhythm. These outcomes were assessed by:

a. exercise tolerance, as measured by the 6-minute walking test (a simple test of exercise performance) at 2 years
b. quality of life [as measured using the EuroQol-5 Dimensions, five-level version (EQ-5D-5L), and the Minnesota Living with Heart Failure (MLWHF) questionnaires] over the 2-year duration of the trial
c. left ventricular diastolic function [as assessed by the ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (E′) (i.e. E/E′ ratio) on echocardiography] at 2 years
d. rates of all-cause hospitalisations during the 2-year follow-up period
e. spontaneous return to sinus rhythm, as measured by electrocardiography, after 2 years of treatment.

All analyses of secondary outcomes (other than hospitalisation rates) were adjusted for the baseline value of each variable. In addition, all major adverse clinical events were recorded, such as death from all causes, death from cardiac causes, hospitalisation for cardiac causes and the occurrence of stroke or systemic thromboembolism. Stata® version 12 (StataCorp LP, College Station, TX, USA) was used for all analyses.

Results

The primary intention-to-treat analysis (imputing the peak VO_2 score at 24 months for those who died with a zero value during the treatment period) peak VO_2 changed from a mean of 14.5 ml/minute/kg (standard deviation 4.6 ml/minute/kg) to a mean of 14.03 ml/minute/kg (standard deviation 5.4 ml/minute/kg) in the spironolactone group and from a mean of 14.6 ml/minute/kg (standard deviation 5.1 ml/minute/kg) to a mean of 14.5 ml/minute/kg (standard deviation 5.1 ml/minute/kg) in the placebo group. The treatment effect showed no difference between the trial groups (differences in means −0.28 ml/minute/kg, 95% confidence interval −1.27 to 0.71 ml/minute/kg; $p = 0.58$). The estimates and confidence intervals for the primary outcome measures were all smaller than the minimal clinically important difference of 2 units used in the sample size calculation, justifying our contention that there is indeed no difference between treatments and it is not the case that the study simply failed to show a difference.

The subgroup analyses showed no significant interaction of the treatment with baseline peak VO_2 values ($\leq$ 16 ml/minute/kg vs. > 16 ml/minute/kg; $p = 0.54$), body mass index (< 25 kg/m^2 vs. 25 to < 30 kg/m^2 vs. $\geq$ 30 kg/m^2; $p = 0.13$), sex ($p = 0.91$) or median blood pressure (i.e. $p = 0.36$ for systolic blood pressure and $p = 0.93$ for diastolic blood pressure).

For secondary efficacy end points, the 6-minute walk test distance increased from a mean of 257 m (standard deviation 83 m) to a mean of 313 m (standard deviation 108 m) in the spironolactone group and from a mean of 270 m (standard deviation 90 m) to a mean of 330 m (standard deviation 112 m) in the placebo group (treatment effect −8.47 m, 95% confidence interval −31.87 to 14.93 m; $p = 0.48$). A measure of left ventricular diastolic function, specifically the E/E′ ratio, changed from a mean of 10.7 (standard deviation 4.4) to a mean of 9.0 (standard deviation 3.1) in the spironolactone arm and from a mean of 10.6 (standard deviation 4.2) to a mean of 9.7 (standard deviation 3.57) in the placebo group (treatment effect −0.68, 95% confidence interval −1.52 to 0.17; $p = 0.12$). Similarly, there was no significant treatment effect difference in B-type natriuretic peptide concentration, which changed from a mean of 164 pg/ml (standard deviation 125 pg/ml) to a mean of 179 pg/ml (standard deviation 171 pg/ml) in the spironolactone group and from a mean of 183 pg/ml (standard deviation 169 pg/ml) to a mean of 186 pg/ml (standard deviation 110 pg/ml) in the placebo group (treatment effect 4.95 pg/ml, 95% confidence interval −28.26 to 38.16 pg/ml; $p = 0.77$). The study treatment was also not associated with a significant treatment effect for quality-of-life scores (i.e. $p = 0.67$ for the EQ-5D-5L questionnaire and $p = 0.84$ for the MLWHF questionnaire).

The estimated glomerular filtration rate was reduced by 6 ml/minute/1.73 m^2 at 2 years in patients allocated to the spironolactone group (with no reduction in those patients receiving placebo; a < 0.001 reduction in *p*-value in the estimated glomerular filtration rate of patients in the spironolactone group compared with those in the placebo group).

Conclusion

Treatment with an aldosterone antagonist, spironolactone, in patients with atrial fibrillation and preserved ejection fraction does not improve exercise tolerance, quality of life and diastolic function.

Future research

The study did not have the power to reliably define the effects of spironolactone in patients with the most severe forms of heart failure with preserved ejection fraction. However, given the significant detrimental effects of the drug in this trial population, further testing of spironolactone in patients with more advanced disease would be difficult to justify.

Trial registration

This trial is registered as ISRCTN10259346. The study is also registered with the European Union Clinical Trials Register as EudraCT number 2014-003702-33 and with ClinicalTrials.gov as NCT02673463. Furthermore, the trial has been adopted by the National Institute for Health Research Clinical Research Network.

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Chapter 1 Introduction

Patients with heart failure (HF) and atrial fibrillation (AF) have a poor prognosis. Major advances have been achieved in the management of patients with HF and reduced left ventricular ejection fraction (LVEF) but there is lack of established treatments for patients with HF with preserved ejection fraction (HFpEF). HF is common in patients with AF with preserved cardiac contractility. In the Framingham Heart Study, 37% of participants with new AF had HF, and the presence of AF was strongly related to incident HFpEF (hazard ratio 2.34).[1] Despite the preservation of LVEF, patients with HFpEF have poor quality of life and high morbidity and mortality.[2] Mineralocorticoid receptor antagonists, such as spironolactone, improve cardiac function and exercise tolerance (and mortality) in patients with HF with a reduced LVEF. However, improvements in morbidity and mortality with conventional treatments used in patients with reduced LVEF have not translated to patients with HFpEF.[3]

Atrial fibrillation represents a separate, clinically and numerically significant, phenotype of HFpEF.[4] The arrhythmia is present in about 40% of people with HFpEF, being associated with higher N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) levels and increased risk of death and hospitalisations related to HF.[5–8]

The mechanisms leading to symptoms, morbidity and mortality in patients with HFpEF and AF are probably related to the disturbed diastolic function that results from lack of atrial stiffness and myocardial fibrosis and stiffening.[9,10] In HFpEF, the diastolic filling is compromised as a result of aggravation in active and passive relaxation (increased cardiac stiffness).[11] This ventricular filling abnormality, in turn, reduces cardiac output and leads to symptoms of HF.[12] This theory is supported by both interventional experiments and large population-based studies carried out using a non-invasive approach to measure diastolic stiffness.[13–15] A stiff ventricle may possess only a limited ability to use the Frank–Starling mechanism to increase stroke volume during exercise with increasing heart rates.[16]

Aldosterone is implicated in cardiac collagen deposition and left ventricular fibrosis.[17] Mechanisms of aldosterone-related cardiac fibrosis include myocardial inflammation, oxidative stress and direct stimulation of cardiac fibroblasts to produce collagen.[18,19] Cardiac expression of mineralocorticoid receptors is increased in AF, thus augmenting the genomic effects of aldosterone.[20]

The effectiveness of spironolactone in HFpEF predominantly related to hypertension has been tested in two clinical trials [i.e. ALDO-DHF (ALDOsterone receptor blockade in Diastolic Heart Failure)[21] and TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist)[22]]. Although 92% of ALDO-DHF trial patients had hypertension only, 5% of the study population ($n = 22$) had AF at presentation.[21] The TOPCAT study[22] involved a higher proportion of patients with AF (mainly paroxysmal AF) but the trial included patients with both preserved LVEF (i.e. $\geq$ 55%) and mild systolic dysfunction (i.e. LVEF $\geq$ 45%).[22] Note that the above studies focused on people who had clearly progressed to the stage of symptomatic HF, rather than the more numerous overall population with permanent AF at risk of developing HF or already exhibiting features of heart failure. Thus, the current evidence on the clinical effectiveness of spironolactone in patients with AF with preserved LVEF on morbidity and quality of life is sparse.

Study objectives

The IMproved exercise tolerance in heart failure with PReserved Ejection fraction by Spironolactone on myocardial fibrosiS in Atrial Fibrillation (IMPRESS-AF) trial aimed to evaluate the effect of mineralocorticoid receptor inhibition with spironolactone on exercise tolerance [assessed as peak oxygen consumption (VO_2) using cardiopulmonary exercise testing] in participants with permanent AF with preserved LVEF compared with placebo (primary outcome), and its effect on quality of life, diastolic function, all-cause hospital admissions and spontaneous return to sinus rhythm (secondary outcomes).

Chapter 2 Methods

The IMPRESS-AF trial is a double-blind, randomised, placebo-controlled single-centre trial conducted in Birmingham, UK. The trial aimed to randomise 250 participants with permanent AF and preserved left ventricular function 1 : 1 to either spironolactone or placebo. The trial protocol was developed following the Standard Protocol Items for Randomized Trials (SPIRIT) statement and the latest patient-reported outcome (PRO)-specific guidance from the International Society for Quality of Life Research's best practice for PROs in clinical trials taskforce.[23–25]

Eligibility

The main inclusion and exclusion criteria are summarised in *Table 1*. Eligible patients were male or female and aged ≥ 50 years. Permanent AF was defined by the European Society of Cardiology's criteria.[26,27] All participants had LVEF ≥ 55% at recruitment, as established by echocardiography during screening.[28] The participants had to be able to perform cardiopulmonary exercise testing using a cycling ergometer and to complete quality-of-life questionnaires in their native language. An interpreter and translated materials were provided if English was not the participant's first language. Average values from 10 consecutive cardiac cycles were calculated to establish the LVEF and the ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (E′) (E/E′ ratio). In patients with hypertension, antihypertensive treatment was established before recruitment. Furthermore, patients with systolic blood pressure > 160 mmHg were excluded.

TABLE 1 Key eligibility criteria

Inclusion	Exclusion
Permanent AF	LVEF < 55% (as determined via echocardiography)
Age ≥ 50 years	Severe systemic illness (with a life expectancy < 2 years)
Ability to understand and complete questionnaires (with or without the use of an interpreter/translated materials)	Severe chronic obstructive pulmonary disease (i.e. requiring home oxygen or chronic oral steroid therapy)
	Severe mitral/aortal valve stenosis/regurgitation
	Significant renal dysfunction (i.e. serum creatinine levels ≥ 220 µmol/l), anuria, active renal insufficiency, rapidly progressing or severe impairment of renal function, confirmed or were diabetic and suspected renal insufficiency/diabetic nephropathy
	Increase in potassium level to > 5 mmol/l
	Recent coronary artery bypass graft surgery (i.e. within 3 months)
	Use of an aldosterone antagonist within 14 days before randomisation
	Use of a potassium-sparing diuretic within 14 days before randomisation
	Systolic blood pressure > 160 mmHg
	Addison's disease
	Hypersensitivity to spironolactone or any of the ingredients in the product
	Any characteristic that may interfere with adherence to the trial protocol

To improve generalisability, the trial did not include a requirement for evidence of diastolic dysfunction, as the trial patients would have impaired diastolic function due to AF. The principal exclusion criteria were designed to exclude patients with contraindications to spironolactone or with significant comorbidities, or that would prevent the prospective participants from completion of the study without relation to the study objectives. All participants received the current optimised treatment following established clinical guidelines on management of AF, HF and hypertension.[12]

Trial setting and identification of participants

The trial was co-ordinated by the Primary Care Clinical Research and Trials Unit (PC-CRTU), which was later merged into the Birmingham Clinical Trials Unit (BCTU), both at the University of Birmingham, Birmingham, UK. The PC-CRTU co-ordinated the participant searches through the National Institute for Health Research (NIHR) Clinical Research Network West Midlands (www.nihr.ac.uk/nihr-in-your-area/west-midlands/; accessed 18 April 2020).

All patients were seen, investigated and managed in the Research Clinic in the Institute of Cardiovascular Sciences (RC-ICS), City Hospital, Birmingham, UK.

Trial participants were recruited from primary care AF registers in general/family practices and outpatient AF clinics in Sandwell and West Birmingham Hospitals Trust, Birmingham, UK. At the screening visit to the RC-ICS, participants were consented into the study and screened for eligibility. During the baseline visit, eligible patients underwent cardiopulmonary exercise testing using a cycling ergometer (to measure peak VO_2) and a 6-minute walk test (6MWT), and completed quality-of-life questionnaires [specifically the validated Minnesota Living with Heart Failure (MLWHF)[29–31] and the EuroQol-5 Dimensions, five-level version (EQ-5D-5L),[32,33] questionnaires].

Randomisation and blinding

Randomisation was performed after baseline assessments were completed using a secure, web-based randomisation system to ensure concealment of allocation. Participants were randomised 1 : 1, stratified by their baseline peak VO_2 (two stratification groups: participants with $VO_2 \leq 16$ ml/minute/kg and participants with $VO_2 > 16$ ml/minute/kg) using a block size of four. The randomisation list was produced by an independent statistician from the trials unit. The system allocated a unique investigational medicinal product number to each participant. Trial participants, the trial team in contact with the patient, care providers, outcome assessors and data analysts all remained blinded to the treatment.

Blinding was achieved by overencapsulating the spironolactone and manufacturing a matching placebo. Spironolactone and placebo were packaged into identical containers that were labelled with the corresponding unique investigational medicinal product number (Catalent Pharma Solutions, Bathgate, UK). The allocation list was known only to the BCTU database programmer and Catalent Pharma Solutions. For the purposes of emergency unblinding, a sealed copy of the randomisation list was kept at the Pharmacy Department at City Hospital, Birmingham, UK (it was independent of the trial, and operated 24 hours a day). The protocol indicated that patients would be withdrawn from the trial treatment if the code was broken, as they would become unblinded to their trial drug.

Treatment and dosing schedule

Participants randomised to spironolactone received 25 mg once daily. This dose has been shown to improve outcomes in systolic HF, improve diastolic function in HFpEF and to reduce collagen turnover, a marker for fibrotic signalling, in the Randomised Aldactone Evaluation Study (RALES) population.[34]

The same dose of spironolactone significantly improved diastolic function within 1 year in participants with HFpEF from the ALDO-DHF trial.[21]

Potassium levels were monitored in all patients. In the case of an increase in potassium level to 5.1–5.5 mmol/l or in the presence of other non-life-threatening side effects (such as gynaecomastia) the trial drug was down-titrated to 25 mg every second day. In such cases, the investigators were advised to re-up-titrate the trial medication if the reason for down-titration had resolved.

Drug toxicity was defined as an increase in potassium level to > 5.5 mmol/l. In the case of toxicity or suspected toxicity, 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. Blood pressure was controlled throughout the duration of the study, with particular attention to blood pressure levels after beginning the study drug and after any changes in antihypertensive agents or their doses.

Follow-up schedule

The participants underwent routine safety follow-up assessments at months 1 and 3 and then 3-monthly thereafter (*Table 2*). The study primary and secondary outcomes were collected at month 24. In addition, the quality-of-life questionnaires were completed after 12 months of study treatment.

Study end points

Primary efficacy end point

The primary efficacy end point was exercise tolerance at 2 years. This was assessed by the difference between trial groups in peak VO_2 on cardiopulmonary exercise testing at 24 months, adjusted for the baseline values.

Secondary efficacy end points

The secondary efficacy end points were quality of life and diastolic function, and also all-cause hospital admissions and spontaneous return to sinus rhythm. These were assessed by:

(a) exercise tolerance, as measured by the 6MWT (a simple test of exercise performance), at 2 years
(b) quality of life (as measured using the MLWHF and EQ-5D-5L[32,33] questionnaires) over the 2-year duration of the study
(c) left ventricular diastolic function (as measured using the E/E′ ratio[35–41] on echocardiography) at 2 years
(d) rates of all-cause hospitalisations during 2 years' follow-up[31,32]
(e) spontaneous return to sinus rhythm on electrocardiography (ECG) after 2 years of treatment.

All analyses of secondary outcomes (other than hospitalisation rates) were adjusted for the baseline value of each variable. In addition, all major adverse clinical events were recorded, such as death from all causes, death from cardiac causes, hospitalisation for cardiac causes, and the occurrence of stroke or systemic thromboembolism.

Adverse events and safety outcomes were collected at all study visits. Prespecified safety outcomes were occurrence of breast pain, breast swelling, allergic reaction, raised serum creatinine levels (> 220 µmol/l), low estimated glomerular filtration rates (eGFRs) (< 30 ml/minute/1.73 m^2) and hyperkalaemia (≥ 5.1 and ≥ 6.0 mmol/l). Changes between baseline and 24 months were estimated and compared for levels of serum creatinine, eGFRs, systolic blood pressure and diastolic blood pressure in each trial arm to

TABLE 2 Timeline of trial procedures and follow-up schedule

	Time point										
			Follow-up								
Trial procedure	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 the patient's blood results showed a potassium level > 5.0 mmol/l									
Eligibility check	✓	✓									
Informed consent	✓										
Relevant medical history taken	✓										
Concomitant medication	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Standard clinical examination, including BP check	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Clinical biochemistry											
Full blood count	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓
Renal function and potassium and sodium levels	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓
HbA_{1c} levels (for diabetics)	✓										
Lipid levels	✓										
Electrocardiography	✓										✓
Echocardiography	✓										✓
BNP test	✓										✓
Randomisation		✓									
Dispensing of study drug		✓			✓		✓		✓		
Cardiopulmonary exercise testing		✓									✓
6MWT		✓									✓
Quality-of-life questionnaires		✓					✓				✓

BNP, B-type natriuretic peptide; BP, blood pressure; HbA_{1c}, glycated haemoglobin.

estimate the magnitude of the impact of the active drug. Spontaneously reported adverse events and serious adverse events were recorded throughout the trial.

Measurement of compliance

Patients' compliance with treatment was determined by computing the percentage of allocated capsules taken across the full 24 months (or up to the date of death). Adequate compliance was defined as $\geq$ 80% allocated capsules taken. Compliance was computed based on prescribing records and returned pill counts. Caution is required when interpreting the compliance data, as partway through the trial it was discovered that errors had been made in the packaging of the drug containers, such that several containers did not contain the correct number of tablets. The recorded returned pill counts did not always appear to match with the expected data range. Compliance is likely to have been underestimated when calculating tablets remaining on withdrawal of patients during the study period.

Statistical analysis

Definition of the intention-to-treat population and imputation rules for the primary outcome

The primary analysis followed 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 participants who died before the 24-month follow-up assessment. For these participants, their peak VO_2 scores at 24 months were imputed as zero values regardless of cause. Although 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 imputation rules were defined prior to any data analysis and reported in the statistical analysis plan.

Sensitivity analyses for different analysis of populations and imputation methods

The following sensitivity analyses were undertaken:

(a) Per-protocol analysis – participants with $\geq$ 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 24-month follow-up assessment.
(c) Multiple imputation – outcomes for participants missing the 24-month 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)[42] method was implemented, which produces imputed values that better match the observed values than linear regression models, especially when peak VO_2 scores are 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, body mass index (BMI), systolic/diastolic blood pressure, 6MWT, B-type natriuretic peptide (BNP) level, E/E′ ratio, EQ-5D-5L scores, 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[43] to obtain a single set of results.

The analyses had been repeated by including additional adjustments for age, sex and BMI at baseline.

Definition of the intention-to-treat population and imputation rules for the secondary outcomes

Analyses of secondary outcomes were performed on the intention-to-treat basis as for the primary outcome. For the 6MWT, the analysis substituted a zero value for those participants who had died before the 24-month follow-up assessment regardless of cause. For the EQ-5D-5L and MLWHF questionnaires at 12 and 24 months, scores indicating the worst level of quality of life observed across the whole data set were substituted for those who had died before the 12- and 24-month follow-up assessment, respectively, regardless of cause; a higher score reflects a poorer quality of life for the MLWHF questionnaire and better quality of life for the EQ-5D-5L. For the MLWHF questionnaire, 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 were undertaken on complete cases only.

Analysis methods

The primary outcome analysis was undertaken using multiple linear regression, including the baseline 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 for the stratifying variable used in the randomisation):

- exercise tolerance measured by 6MWT at 2 years
- quality of life as measured by the MLWHF and EQ-5D-5L questionnaires at 1 and 2 years
- left ventricular diastolic function as measured by the E/E′ ratio at 2 years
- BNP level at 2 years.

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

Multiple logistic regression was carried out, analysing the spontaneous return to sinus rhythm (on the ECG) at 2 years, adjusting only for baseline continuous peak VO_2 score. An additional analysis was undertaken, adjusting for the log-transformed BNP level at baseline, as this is known to be predictive of this outcome. The treatment effect estimate was an odds ratio (odds on spironolactone compared with placebo), with the uncertainty expressed using a 95% CI.

A Cox regression model was used to analyse the time-to-hospitalisation event data (for any cause) over 2 years, adjusted for baseline continuous peak VO_2 score. Data on participants who had not been hospitalised over the 2-year period were censored at the date of their last attendance for clinical events; those who died who 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 for any cause was presented. The treatment effect estimate was a hazard ratio (hazard on spironolactone compared with placebo), with the uncertainty expressed using a 95% CI.

Subgroup analyses for primary outcome

The following predefined subgroups at baseline were compared with 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 – ≤ 16 vs. > 16 ml/minute/kg
- sex – male versus female
- age groups (years) – split at median
- BMI groups – < 25 kg/m^2 (normal or underweight), 25–30 kg/m^2 (overweight) and ≥ 30 kg/m^2 (obese)
- systolic blood pressure groups (mmHg) – split at median
- diastolic blood pressure groups (mmHg) – split at median.

Analysis of adverse events and known safety issues

Any cases of major adverse clinical events were recorded, such as:

- death from all causes
- death from cardiac causes
- hospitalisation for cardiac causes
- stroke
- systemic thromboembolism.

Major adverse clinical events were compared between the two treatment groups using Fisher's exact test.

Absolute changes in creatinine, eGFR, systolic blood pressure and diastolic blood pressure from baseline to 24 months were computed within each trial arm, and compared as a difference in mean change between trial arms (with statistical significance assessed using a *t*-test).

The known safety issues with the intervention drug were assessed at each visit and reported by trial arm. Formal comparisons had not been undertaken. The known safety issues were as follows:

- eGFR < 30 ml/minute/1.73 m^2
- hyperkalaemia (≥ 5.1 mmol/l)
- hyperkalaemia (≥ 6.0 mmol/l)
- creatinine level > 220 µmol/l
- breast pain
- breast swelling
- allergic reaction to the trial medication.

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

Stata® version 12 (StataCorp LP, College Station, TX, USA) was used for all analyses.

Deviations from the protocol

The statistical analysis plan was refined prior to data analysis and compared with methods stated in the protocol. The key differences are:

1. The outcomes are defined as 'differences in final values' rather than 'improvement in final values'. This is mainly a semantic change, as the prespecified model always included adjustment for baseline variables rather than the outcome being a change score. It also was considered a preferable wording as it is a non-directional hypothesis.
2. The final model did not include GP practice as a random effect as the numbers recruited from each practice were very small.
3. Adjustment for baseline blood pressure values was not included as these values were not considered prognostic of outcome.
4. Repeated measures models were not used for the small number of quality-of-life outcomes that were assessed at both time points; the study authors preferred to use separate estimates at 6 and 12 months as this allowed for estimation of treatment effects at both time points.
5. Subgroup (interaction) effects were considered only for the primary outcome. The variables investigated were determined by the Trial Management Group prior to any data analysis.
6. The New York Heart Association (NYHA) class analysis was not undertaken because of difficulties in obtaining the required data.

Sample size

The sample size required to show a clinically important difference in the primary outcome of peak VO_2 was determined. Published values of peak VO_2 in subjects with HF give a mean baseline value of 16 ml/minute/kg [standard deviation (SD) 5 ml/minute/kg][44] and data for HFpEF suggest that a difference of 2 ml/minute/kg would be clinically relevant. These data were used for the design of the recent ALDO-DHF study of spironolactone in patients with HFpEF, 95% of whom were free from AF.[21,45] Unfortunately, the study by Cicoira *et al.*,[44] used for power calculation does not give a SD in peak VO_2; however, a similar trial, Edelmann *et al.*[46] provides that statistic (i.e. 5 ml/minute/kg) and also reports a similar magnitude of the effect. A sample size of 100 participants in each trial 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 using a 5% two-sided statistical significance level. The sample size was increased to 125 participants per arm for provision for a 20% dropout rate. Statistical power would be higher should this rate be too pessimistic, and with the benefits of adjusting for baseline values.

Key changes to the protocol

1 May 2015

Inclusion in the trial is no longer conditional on the patient having normal BNP levels (i.e. < 100 pg/ml). The amendment was based on failure to identify suitable participants when this inclusion criterion was applied.

5 January 2017

The threshold of potassium for withdrawal, as a result of hyperkalaemia, increased from > 5.5 mmol/l to > 6.0 mmol/l. The amendment was based on current practice for use of spironolactone.

Study funding and management

The IMPRESS-AF trial was funded by the NIHR, UK. The University of Birmingham is the sponsor of this trial. The day-to-day management of the trial was co-ordinated by the PC-CRTU/BCTU at the University of Birmingham, Birmingham, UK, and registered by the 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. The study design was helped by a patient representative, who reviewed the study proposal and provided their comments (which were included in the proposal). Another patient representative was a member of the Trial Steering Committee, but no comments or criticisms were received from them.

Study ethics

The study was approved by the National Research and Ethics Committee (REC) West Midlands – Coventry and Warwickshire (REC reference number 14/WM/1211). All participants provided signed informed consent.

Trial registration

The study was registered with the European Union Clinical Trials Register (EudraCT number 2014-003702-33) and with ClinicalTrials.gov (NCT02673463), and has been adopted by the NIHR Clinical Research Network.

Chapter 3 Results

A total of 250 patients were randomised to spironolactone or placebo (125 patients per group) between October 2014 and June 2016 (in accordance with the projected recruitment completion date, 30 June 2016). Two-year follow-up was completed in June 2018. Patients were elderly (mean age 72.3 years, SD 7.4 years), with a mean BMI of 30.5 kg/m^2 (SD 5.4 kg/m^2) and predominantly male (76.4%) and of white ethnicity (94.4%). The trial arms appear to be well balanced on all important variables (*Table 3*). Results are presented in accordance with the Consolidated Standards of Reporting Trials (CONSORT) and CONSORT PRO guidelines.[47] The final study visit was attended by 101 (81%) patients randomised to the spironolactone group and 106 (85%) patients randomised to placebo (*Figure 1*).

TABLE 3 Baseline characteristics

Characteristic	Trial arm		Overall (*N* = 250)
	Spironolactone (*N* = 125)	Placebo (*N* = 125)	
Stratification variables			
Peak VO_2 (ml/minute/kg)[a]			
≤ 16 ml, *n* (%)	77 (61.6)	78 (62.4)	155 (62.0)
> 16 ml, *n* (%)	48 (38.4)	47 (37.6)	95 (38.0)
Mean (SD)	14.5 (4.6)	14.6 (5.1)	14.5 (4.8)
Median (IQR)	13.9 (10.8–18.3)	14.4 (10.8–17.5)	14.1 (10.8–17.8)
Missing, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Demographic and other baseline variables			
Age (years)			
Mean (SD)	72.4 (7.1)	72.3 (7.9)	72.3 (7.4)
Median (IQR)	72.8 (68.3–77.2)	72.4 (67.4–77.6)	72.6 (67.6–77.6)
Missing, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
BMI (kg/m^2)			
Mean (SD)	30.4 (5.2)	30.5 (5.6)	30.5 (5.4)
Median (IQR)	29.1 (26.4–33.2)	30.1 (26.1–33.9)	29.7 (26.3–33.3)
Missing, *n* (%)	0 (0.0)	2 (1.6)	2 (0.8)
Sex, *n* (%)			
Female	28 (22.4)	31 (24.8)	59 (23.6)
Male	97 (77.6)	94 (75.2)	191 (76.4)
Missing	0 (0.0)	0 (0.0)	0 (0.0)

continued

TABLE 3 Baseline characteristics (*continued*)

Characteristic	Trial arm		
	Spironolactone (*N* = 125)	Placebo (*N* = 125)	Overall (*N* = 250)
Current medication, *n* (%)			
Yes	123 (98.4)	124 (99.2)	247 (98.8)
No	2 (1.6)	0 (0.0)	2 (0.8)
Missing	0 (0.0)	1 (0.8)	1 (0.4)
Smoking status, *n* (%)			
Current smoker	6 (4.8)	8 (6.4)	14 (5.6)
Ex-smoker	66 (52.8)	68 (54.4)	134 (53.6)
Non-smoker	53 (42.4)	49 (39.2)	102 (40.8)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Alcohol use (units per week)			
Mean (SD)	7.2 (9.9)	8.8 (10.8)	8.0 (10.4)
Median (IQR)	3.0 (0.0–12.0)	6.0 (0.0–14.0)	4.0 (0.0–13.0)
Missing, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
6MWT (metres)			
Mean (SD)	256.7 (83.4)	270.4 (89.5)	263.6 (86.6)
Median (IQR)	266.0 (196.0–316.0)	271.0 (200.0–330.0)	266.0 (200.0–322.0)
Missing, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Resting heart rate (b.p.m.)			
Mean (SD)	87.3 (19.4)	86.7 (18.7)	87.0 (19.0)
Median (IQR)	85.0 (74.0–99.0)	83.0 (74.0–97.0)	84.0 (74.0–97.0)
Missing, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Peak heart rate during CPET (b.p.m.)			
Mean (SD)	128.4 (26.1)	129.9 (25.4)	129.1 (25.7)
Median (IQR)	129.0 (109.0–150.0)	126.0 (112.0–148.0)	127.0 (110.0–149.0)
Missing, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity, *n* (%)			
White	118 (94.4)	118 (94.4)	236 (94.4)
Mixed	1 (0.8)	0 (0.0)	1 (0.4)
Black	3 (2.4)	3 (2.4)	6 (2.4)
Asian	3 (2.4)	2 (1.6)	5 (2.0)
Other ethnic group	0 (0.0)	2 (1.6)	2 (0.8)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
BNP concentration (pg/ml)			
Mean (SD)	163.5 (125.4)	183.3 (168.5)	173.4 (148.5)
Median (IQR)	122.0 (73.0–230.0)	136.0 (81.7–241.0)	127.0 (77.9–236.0)
Missing, *n* (%)	0 (0.0)	1 (0.8)	1 (0.4)

TABLE 3 Baseline characteristics (*continued*)

Characteristic	Trial arm		
	Spironolactone (*N* = 125)	Placebo (*N* = 125)	Overall (*N* = 250)
Systolic blood pressure (mmHg)			
Mean (SD)	129.2 (15.5)	130.1 (15.0)	129.6 (15.3)
Median (IQR)	130.0 (117.0–140.0)	129.0 (118.0–142.0)	129.0 (117.0–140.0)
Missing, *n* (%)	0 (0.0)	1 (0.8)	1 (0.4)
Diastolic blood pressure (mmHg)			
Mean (SD)	75.7 (10.9)	75.6 (13.9)	75.7 (12.5)
Median (IQR)	75.0 (67.0–83.0)	74.0 (68.0–82.0)	74.0 (68.0–82.0)
Missing, *n* (%)	0 (0.0)	1 (0.8)	1 (0.4)
Waist circumference (cm)			
Mean (SD)	99.5 (12.5)	100.3 (14.4)	99.9 (13.5)
Median (IQR)	99.0 (91.4–106.7)	101.0 (91.0–106.7)	99.1 (91.4–106.7)
Missing, *n* (%)	0 (0.0)	2 (1.6)	2 (0.8)
Hip circumference (cm)			
Mean (SD)	107.4 (10.0)	108.0 (13.2)	107.7 (11.7)
Median (IQR)	106.7 (101.0–112.0)	106.7 (100.0–114.3)	106.7 (100.0–114.3)
Missing, *n* (%)	0 (0.0)	2 (1.6)	2 (0.8)
Left ventricular ejection fraction (%)			
Mean (SD)	60.4 (5.4)	60.5 (5.7)	60.5 (5.5)
Median (IQR)	58.0 (56.6–62.0)	58.0 (56.3–63.0)	58.0 (56.4–63.0)
Missing, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Mitral valve measurement: E/E′ ratio			
Mean (SD)	10.7 (4.4)	10.6 (4.2)	10.7 (4.3)
Median (IQR)	9.8 (8.0–12.0)	9.7 (7.5–13.0)	9.8 (7.8–12.6)
Missing, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
EQ-5D-5L score			
Mean (SD)	0.81 (0.19)	0.83 (0.16)	0.82 (0.18)
Median (IQR)	0.84 (0.74–0.94)	0.88 (0.74–0.94)	0.87 (0.74–0.94)
Missing, *n* (%)	4 (3.2)	5 (4.0)	9 (3.6)
MLWHF score[b]			
Mean (SD)	22.9 (20.4)	21.9 (22.9)	22.4 (21.7)
Median (IQR)	17.0 (6.3–35.8)	14.0 (5.8–30.0)	14.0 (6.0–33.8)
Missing, *n* (%)	8 (6.4)	4 (3.2)	12 (4.8)

b.p.m., beats per minute; CPET, cardiopulmonary exercise test; IQR, interquartile range.

a The dichotomised peak VO_2 score (ml/minute/kg) was used as the stratification variable.

b To score the MLWHF questionnaire, at most 20% of the 21 responses were allowed to be missing, which was equivalent to four data items. If there were ≤ 4 data items missing, then mean substitution was used to impute the missing responses. The questionnaire was scored by summating the responses to all 21 questions; otherwise, the person's score was left missing.

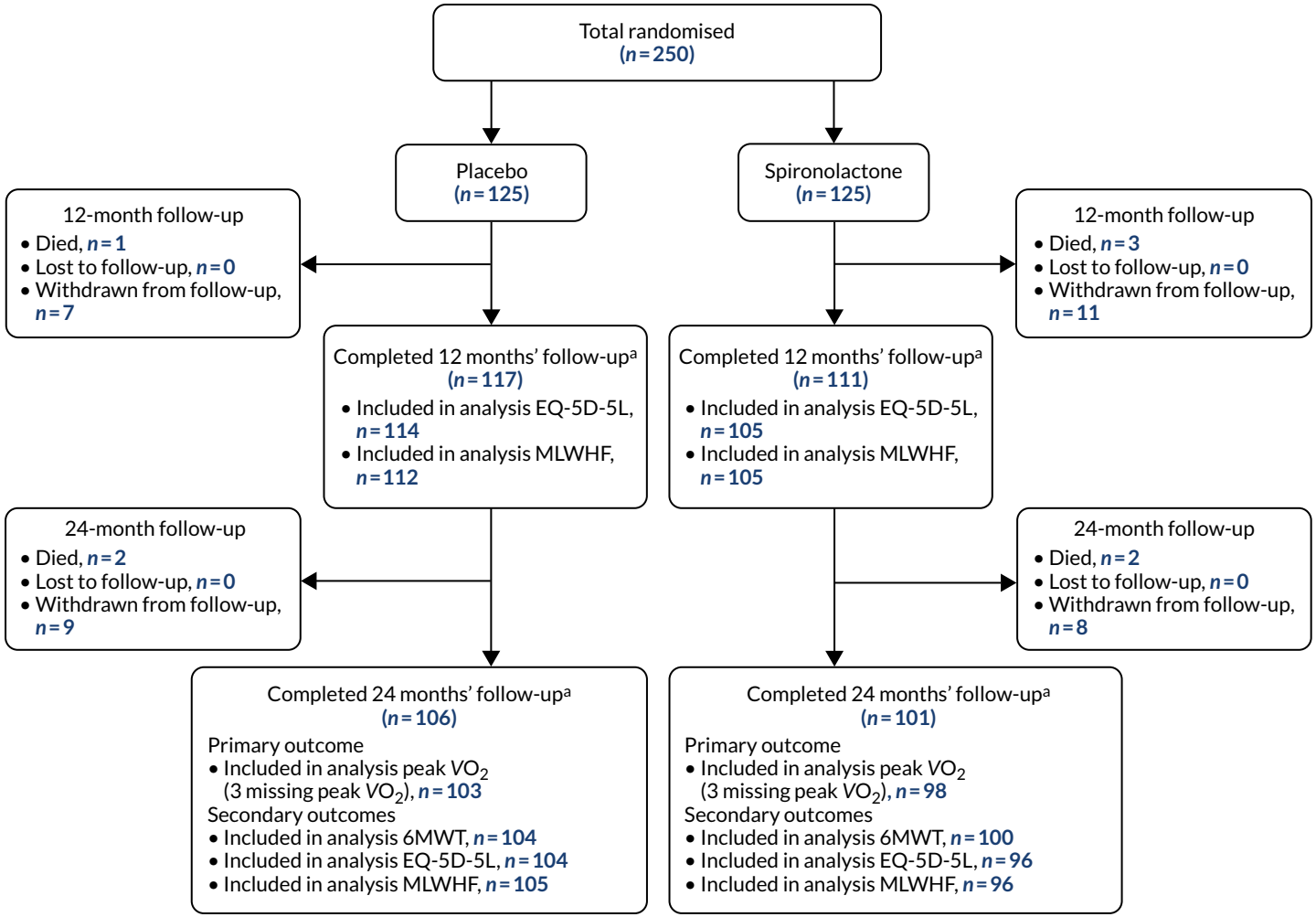

FIGURE 1 The CONSORT flow diagram. a, Figures include participants who discontinued the investigational medicinal product, but provided data.

Primary outcome

The data on the primary outcome, peak VO_2, at the end of the trial were analysed for the available 106 patients in the placebo group and 103 patients in the spironolactone group (*Table 4* and *Appendix 1*). In both trial arms, three patients were not able to perform a cardiopulmonary exercise test (CPET) because of frailty. In the primary intention-to-treat analysis (imputing the peak VO_2 score at 24 months for the three placebo and five spironolactone group patients who died with a zero value during the treatment period), peak VO_2 changed from a mean of 14.5 ml/minute/kg (SD 4.6 ml/minute/kg) to a mean of 14.03 ml/minute/kg (SD 5.4 ml/minute/kg) in the spironolactone group ($n = 103$) and from a mean of 14.6 ml/minute/kg (SD 5.1 ml/minute/kg) to a mean of 14.5 ml/minute/kg (SD 5.1 ml/minute/kg) in the placebo group ($n = 106$). The treatment effect showed no difference between the trial groups (differences in means −0.28 ml/minute/kg, 95% CI −1.27 to 0.71 ml/minute/kg; $p = 0.58$). The estimates and CIs for primary outcome measures were all smaller than the minimal clinically important difference of 2 units used in the sample size calculation, which provides a basis for claiming that the study has proven no difference rather than just failing to show a difference. The findings were consistent across the sensitivity analyses performed (see *Table 4*).

TABLE 4 Primary outcome results [peak VO_2 (ml/minute/kg)[a] at 24 months]

	Trial arm					
	Spironolactone		Placebo		Treatment effect (95% CI)[c]	*p*-value[c]
Analysis	Mean (SD)[b]	*n*	Mean (SD)[b]	*n*		
Primary analysis[d] (adjusted for stratification variable)	14.03 (5.38)	103	14.45 (5.14)	106	−0.28 (−1.27 to 0.71)	0.58
Sensitivity analysis (adjusted for stratification variable)						
Per-protocol analysis[e]	14.84 (4.32)	57	14.88 (4.90)	77	0.21 (−0.78 to 1.21)	0.67
Complete-case analysis	14.75 (4.45)	98	14.87 (4.57)	103	−0.09 (−0.86 to 0.68)	0.81
Multiple imputation method[f]	13.39 (6.04[g])	125	14.02 (5.48[g])	125	−0.53 (−1.57 to 0.51)	0.32
Sensitivity analysis (additionally adjusted for age, sex and BMI)						
Primary analysis with the additional adjustment	14.03 (5.38)	103	14.47 (5.16)	105	−0.32 (−1.32 to 0.68)	0.53
Per-protocol analysis[e]	14.84 (4.32)	57	14.91 (4.92)	76	0.17 (−0.81 to 1.14)	0.73
Complete-case analysis	14.75 (4.45)	98	14.89 (4.59)	102	−0.14 (−0.89 to 0.61)	0.71
Multiple imputation method[f]	13.39 (6.04[g])	125	14.02 (5.48[g])	125	−0.53 (−1.57 to 0.51)	0.31

a VO_2 refers to oxygen consumption.
b The mean is a crude mean.
c 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 VO_2 score. In the sensitivity analyses additional adjustments for age, sex and BMI were made.
d A value of zero was assigned to peak VO_2 score for those patients who died before the 24-month follow-up assessment.
e The per-protocol population was defined as ≥ 80% of capsules taken across the full 24 months' trial duration or up to the time of death.
f The PMM imputation method was used to generate 20 imputed data sets. Data for participants in the spironolactone group and the placebo group were imputed separately. Peak VO_2, age, BMI, systolic/diastolic blood pressure, 6MWT, BNP level, E/E′ ratio, EQ-5D-5L and MLWHF scores at baseline and sex were included in the imputation model.
g Estimates of the SD have been obtained by multiplying the standard error by the square root of 125.

The subgroup analyses (*Table 5*) showed no significant interaction of the treatment with baseline peak VO_2 values (≤ 16 ml/minute/kg vs. > 16 ml/minute/kg; $p = 0.535$), BMI (< 25 vs. 25–30 vs. ≥ 30 kg/m^2; $p = 0.131$), sex ($p = 0.906$) and median blood pressure ($p = 0.358$ for systolic blood pressure and $p = 0.926$ for diastolic blood pressure). There was a significant interaction between the treatment and age, evaluated by splitting the study population by median age (72.6 years): higher peak VO_2 values were observed in older patients in the spironolactone group ($p = 0.025$ for the 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.

TABLE 5 Subgroup analysis of the primary outcome

	Trial arm						
	Spironolactone		Placebo				
Analyses	Mean (SD)[a]	*n*	Mean (SD)[a]	*n*	Treatment effect (95% CI)[b]	Estimate of difference (95% CI)[b,c]	*p*-value for interaction[b]
Peak VO_2 (ml/minute/kg)							
≤ 16	11.15 (4.39)	60	11.87 (3.73)	63	−0.56 (−1.85 to 0.73)	0.64 (−1.38 to 2.66)	0.54
> 16	18.05 (3.86)	43	18.23 (4.58)	43	0.07 (−1.47 to 1.62)		
Age (years)							
≤ median[d]	14.38 (6.25)	54	16.61 (4.78)	53	−1.40 (−2.76 to −0.05)	2.24 (0.28 to 4.20)	0.025
> median	13.65 (4.26)	49	12.29 (4.58)	53	0.83 (−0.55 to 2.22)		
BMI (kg/m^2)							
< 25	14.71 (3.92)	14	15.18 (4.85)	14	0.30 (−2.40 to 2.99)	–	0.13
25–30	14.91 (6.47)	43	16.37 (4.98)	36	−1.59 (−3.21 to 0.02)	−1.89 (−5.05 to 1.27)	
≥ 30	13.01 (4.49)	46	13.04 (5.00)	55	0.58 (−0.85 to 2.00)	0.28 (−2.79 to 3.35)	
Sex (*n*)							
Female	10.95 (3.73)	20	12.07 (2.87)	26	−0.41 (−2.54 to 1.72)	0.14 (−2.28 to 2.57)	0.91
Male	14.77 (5.47)	83	15.22 (5.48)	80	−0.27 (−1.39 to 0.86)		
Systolic blood pressure (mmHg)							
≤ median[d]	13.46 (6.22)	52	14.78 (5.23)	54	−0.71 (−2.10 to 0.68)	0.93 (−1.06 to 2.93)	0.36
> median	14.62 (4.36)	51	13.99 (5.05)	51	0.23 (−1.19 to 1.64)		
Diastolic blood pressure (mmHg)							
≤ median[d]	13.45 (5.63)	54	13.67 (5.17)	58	−0.24 (−1.58 to 1.11)	−0.09 (−2.08 to 1.90)	0.93
> median	14.68 (5.08)	49	15.29 (5.01)	47	−0.33 (−1.78 to 1.12)		

a The mean is unadjusted.
b 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 VO_2 score.
c The lower level was always treated as the reference group for the estimates of treatment difference, apart from sex, for which female was the reference group.
d The median age is 72.58 years, the median systolic blood pressure is 129 mmHg and the median diastolic blood pressure is 74 mmHg.

Note
The placebo group is the reference group.

Secondary outcomes

For the secondary efficacy end points, the 6MWT distance increased from a mean of 257 m (SD 83 m) to a mean of 313 m (SD 108 m) in the spironolactone group and from a mean of 270 m (SD 90 m) to a mean of 330 m (SD 112 m) in the placebo group (treatment effect −8.47 m, 95% CI −31.87 to 14.93 m; $p = 0.48$) (*Table 6*). A measure of left ventricular diastolic function, the E/E′ ratio, changed from a mean of

TABLE 6 Secondary outcomes and BNP concentration (continuous variables)

		Trial arm					
		Spironolactone		Placebo		Treatment effect (95% CI)[b]	*p*-value[b]
Analyses	End point	Mean (SD)[a]	*n*	Mean (SD)[a]	*n*		
Primary analysis (adjusted for stratification variable)							
6MWT (metres)	24 months[c]	312.90 (108.12)	105	330.43 (112.16)	107	−8.47 (−31.87 to 14.93)	0.48
LV diastolic function as measured by the E/E′ ratio	24 months	9.00 (3.05)	101	9.72 (3.57)	106	−0.68 (−1.52 to 0.17)	0.12
BNP concentration (pg/ml)	24 months	179.43 (170.55)	101	185.61 (109.65)	105	4.95 (−28.26 to 38.16)	0.77
EQ-5D-5L	12 months[d]	0.83 (0.21)	106	0.84 (0.18)	111	−0.009 (−0.049 to 0.032)	0.67
	24 months[d]	0.82 (0.24)	98	0.84 (0.20)	104	−0.007 (−0.051 to 0.038)	0.77
MLWHF[e]	12 months[f]	18.44 (20.89)	101	16.90 (17.76)	110	1.24 (−2.48 to 4.96)	0.51
	24 months[f]	17.39 (22.72)	96	15.34 (20.35)	104	0.49 (−4.32 to 5.29)	0.84
Secondary analysis (additionally adjusted for age, sex and BMI)							
6MWT (metres)	24 months[c]	312.90 (108.12)	105	331.13 (112.46)	106	−8.30 (−31.89 to 15.28)	0.49
LV diastolic function as measured by the E/E′ ratio	24 months	9.00 (3.05)	101	9.69 (3.57)	105	−0.64 (−1.48 to 0.20)	0.13
BNP concentration (pg/ml)	24 months	179.43 (170.55)	101	187.13 (109.06)	104	4.37 (−28.53 to 37.28)	0.79
EQ-5D-5L	12 months[d]	0.83 (0.21)	106	0.85 (0.18)	109	−0.006 (−0.047 to 0.034)	0.75
	24 months[d]	0.82 (0.24)	98	0.84 (0.20)	103	−0.004 (−0.049 to 0.041)	0.88
MLWHF[e]	12 months[f]	18.44 (20.89)	101	16.29 (17.32)	108	1.35 (−2.40 to 5.10)	0.48
	24 months[f]	17.39 (22.72)	96	15.29 (20.44)	103	0.27 (−4.60 to 5.14)	0.91

LV, left ventricular.

a The mean is a crude mean.

b The mean differences between the spironolactone group and the placebo group, 95% CIs and the corresponding *p*-values were estimated from linear regression models, after adjustment for the baseline continuous peak VO_2 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.

c A value of zero was assigned to those patients who died before the 24-month follow-up assessment regardless of cause.

d The lowest value across all participants was assigned to those who died before the 12-month follow-up assessments. Similarly, the lowest score value across all participants was assigned to those who died before the 24-month follow-up.

e MLWHF scores ranged from 0 to 105, with a higher score reflecting a poorer quality of life.

f The highest score value across all participants was assigned to those who died before the 12-month follow-up assessment. Similarly, the lowest score value across all participants was assigned to those who died before the 24-month follow-up.

Note

The placebo group is the reference group.

10.7 (SD 4.4) to a mean of 9.0 (SD 3.1) in the spironolactone group and from a mean of 10.6 (SD 4.2) to a mean of 9.7 (SD 3.57) in the placebo group (treatment effect −0.68, 95% CI −1.52 to 0.17; $p = 0.12$). Similarly, there was no significant treatment effect differences in BNP concentration, which changed from a mean of 164 pg/ml (SD 125 pg/ml) to a mean of 179 pg/ml (SD 171 pg/ml) in the spironolactone group and from a mean of 183 pg/ml (SD 169 pg/ml) to a mean of 186 pg/ml (SD 110 pg/ml) in the placebo group (treatment effect 4.95 pg/ml, 95% CI −28.26 to 38.16 pg/ml; $p = 0.77$). The study treatment was also not associated with significant treatment effect for quality-of-life scores (a *p*-value of 0.77 for the EQ-5D-5L questionnaire and a *p*-value of 0.84 for the MLWHF questionnaire) (see *Table 6*). The findings remained consistent after additional adjustment of age, sex and BMI for all outcomes.

Spontaneous return to sinus rhythm as demonstrated by ECG performed after 2 years of treatment was uncommon in both study groups [four participants (3.8%) in the placebo group and eight participants (7.9%) in the spironolactone group; $p = 0.21$] (*Table 7*). Further adjustment for log-transformed BNP level at baseline made little difference.

TABLE 7 Secondary outcomes: spontaneous return to sinus rhythm (as assessed via an ECG) at 2 years

	Trial arm			
Analyses	**Spironolactone**	**Placebo**	**Odds ratio (95% CI)[a]**	***p*-value[a]**
Primary analysis (adjusted for stratification variable)				
Total (*n*)	101	106	2.19 (0.64 to 7.52)	0.21
Yes,[b] *n* (%)	8 (7.9)	4 (3.8)		
No, *n* (%)	93 (92.1)	102 (96.2)		
Secondary analysis (additionally adjusted for the log-transformed BNP level at baseline)				
Total (*n*)	101	105	2.15 (0.63 to 7.38)	0.23
Yes,[b] *n* (%)	8 (7.9)	4 (3.8)		
No, *n* (%)	93 (92.1)	101 (96.2)		
Secondary analysis (additionally adjusted for age, sex and BMI)				
Total (*n*)	101	105	2.14 (0.62 to 7.35)	0.23
Yes,[b] *n* (%)	8 (7.9)	4 (3.8)		
No, *n* (%)	93 (92.1)	101 (96.2)		
Secondary analysis (additionally adjusted for the log-transformed BNP level at baseline, age, sex and BMI)				
Total (*n*)	101	104	2.09 (0.61 to 7.20)	0.24
Yes,[b] *n* (%)	8 (7.9)	4 (3.9)		
No, *n* (%)	93 (92.1)	100 (96.2)		

a The odds ratios, 95% CIs and the corresponding *p*-values were estimated from a logistic regression model, after adjustment for the continuous peak VO_2 and BNP level score at baseline for the primary analysis and were additionally adjusted for age, sex and BMI for the secondary analysis.
b 'Yes' means spontaneous return to sinus rhythm (as assessed via an ECG) after 2 years of treatment.
Note
The placebo group is the reference group.

Other outcomes

At least one hospitalisation for any reason was observed in 15.3% of patients in the spironolactone group and 22.8% in the placebo group ($p = 0.15$; $p = 0.12$ after adjustment for age, sex and BMI) (*Table 8* and *Figure 2*). Three patients were admitted more than once (*Table 9*). There was no significant difference in overall mortality, death from cardiac causes, hospitalisations due to cardiac causes, and rates of stroke and systemic thromboembolism between the trial arms (*Table 10*).

TABLE 8 Secondary outcomes: hospitalisation for all causes

	Trial arm							
	Spironolactone			Placebo				
Analyses	*n*	Participants with at least one event, *n* (%)	Incidence rate (number per 10,000 person-days)	*n*	Participants with at least one event, *n* (%)	Incidence rate (number per 10,000 person-days)	Hazard ratio (95% CI)[a]	*p*-value[a]
Primary analysis (adjusted for stratification variable)								
Hospitalisation for all causes	118	18[b] (15.3)	2.46	123	28 (22.8)	3.78	0.65 (0.36 to 1.17)	0.15
Secondary analysis (additionally adjusted for age, sex and BMI)								
Hospitalisation for all causes	118	18[b] (15.3)	2.46	121	27[c] (22.3)	3.69	0.62 (0.34 to 1.14)	0.12

a The adjusted hazard ratio, 95% CIs and the corresponding *p*-values were estimated from a Cox regression model adjusting for the baseline continuous peak VO_2 scores for the primary analysis and were additionally adjusted for age, sex and BMI for the secondary analysis. The placebo group is the reference group.
b There was one first hospitalised event that was entered onto the follow-up table, but had no date; this event was excluded from the time-to-event analysis.
c One participant had been hospitalised, but was missing a BMI measurement at baseline, so was excluded from secondary analysis.

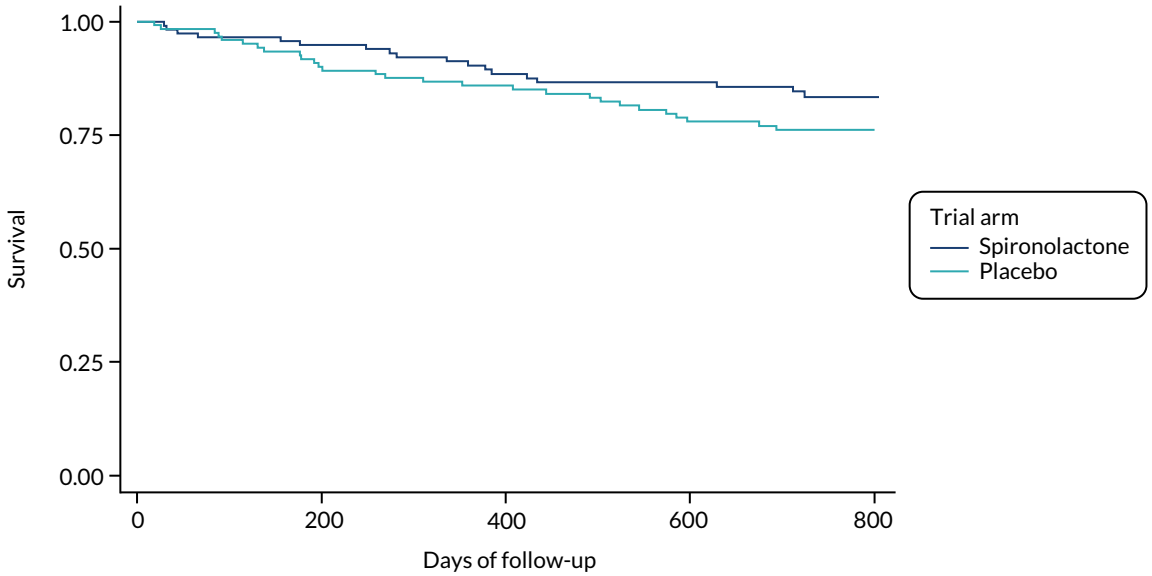

FIGURE 2 Kaplan–Meier plot of time to first hospitalisation.

TABLE 9 Number of hospitalisations per participant by trial arm

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

TABLE 10 Adverse events[a] and serious adverse events

AEs/SAEs	Trial arm		
	Spironolactone (*n* = 125)	Placebo (*n* = 125)	*p*-value[b]
All SAEs			
Total number of patients experiencing at least one SAE, *n* (%)	23 (18.4)	32 (25.6)	
Total number of SAEs	27	42	
Prespecified major adverse clinical events (SAEs)*, n *(%)	***(n = 121[c])***	***(n = 123[c])***	
Death from all causes	5 (4.1)	3 (2.4)	0.50
Death from cardiac causes	5[d] (4.1)	1 (0.8)	0.12
Hospitalisation for cardiac causes	2 (1.7)	6[e] (4.9)	0.28
Stroke	0 (0.0)	2 (1.6)	0.50
Systemic thromboembolism	0 (0.0)	1 (0.8)	1.00
Prespecified safety outcomes (AEs)* , n *(%) *Number of patients experiencing at least one episode*			
Breast pain	17 (13.6)	5 (4.0)	
Breast swelling	11 (8.8)	4 (3.2)	
Allergic reaction	2 (1.6)	0 (0.0)	
Hyperkalaemia (≥ 5.1 mmol/l)	46 (36.8)	17 (13.6)	
Hyperkalaemia (≥ 6.0 mmol/l)	3 (2.4)	0 (0.0)	
Serum creatinine level > 220 µmol/l	1 (0.8)	0 (0.0)	
eGFR < 30 ml/minute/1.73 m^2	8 (6.4)	2 (1.6)	
Total number of episodes			
Breast pain	40	9	
Breast swelling	26	10	
Allergic reaction	2	0	

TABLE 10 Adverse events[a] and serious adverse events (*continued*)

AEs/SAEs	Trial arm		*p*-value[b]
	Spironolactone ($n = 125$)	Placebo ($n = 125$)	
Hyperkalaemia (≥ 5.1 mmol/l)	72	30	
Hyperkalaemia (≥ 6.0 mmol/l)	3	0	
Serum creatinine level > 220 µmol/l	1	0	
eGFR < 30 ml/minute/1.73 m^2	8	2	

AE, adverse event; SAE, serious adverse event.
a AEs reported were collected at follow-up visits.
b *p*-values were obtained using Fisher's exact test for major adverse clinical events.
c Six SAEs (occurring in six individuals) were missing on their adjudication results; therefore, the corresponding outcomes for major adverse clinical events were missing, in which four participants were in the spironolactone group and two in the placebo group. Where applicable, these six participants were not included in the Fisher's exact test and the corresponding percentage calculation.
d One participant died from cardiac causes but also had one SAE not adjudicated; so in this case only three participants were missing in the spironolactone group. The denominator used for the percentage calculation was 122.
e One participant in the placebo group had two hospitalisations for cardiac causes, so only one SAE was counted for this participant.

Compliance with the allocated treatment with at least 80% of capsules taken was recorded in 58 (46.4%) participants in the spironolactone group and 80 (64.0%) in the placebo group. Among patients randomised to the spironolactone group systolic blood pressure fell by −7.2 mmHg (95% CI −12.3 to −2.2 mmHg) after 2 years of treatment, whereas there was almost no change in blood pressure in the placebo group (*Table 11* and *Appendix 2*). There was no significant treatment effect for diastolic blood pressure. Spironolactone increased serum creatinine levels by 6.9 µmol/l (95% CI 3.4 to 10.5 µmol/l) and lowered eGFR by 6 ml/minute/1.73 m^2 (95% CI −9.3 to −2.8 ml/minute/1.73 m^2) after 2 years' treatment. Deviations from the study protocol are reported in *Appendix 3*.

TABLE 11 Changes in clinical characteristics

Changes in clinical characteristics	Trial arm				Mean difference (95% CI)[a]	*p*-value[a]
	Spironolactone		Placebo			
	Mean (SD)	*n* (%)	Mean (SD)	*n* (%)		
Exploratory outcomes (changes in clinical characteristics)						
Serum creatinine (µmol/l)						
Baseline	90.20 (23.45)	125 (100)	90.20 (20.22)	125 (100)		
24 months	98.95 (23.30)	101 (80.8)	91.64 (21.47)	106 (84.8)		
Change from baseline to 24 months	8.88 (13.75)	101 (80.8)	1.96 (12.14)	106 (84.8)	6.92 (3.37 to 10.47)	0.0002
eGFR (ml/minute/1.73 m^2)						
Baseline	70.25 (16.40)	125 (100)	68.55 (16.64)	125 (100)		
24 months	63.59 (15.13)	101 (80.8)	68.61 (13.98)	106 (84.8)		
Change from baseline to 24 months	−6.82 (11.34)	101 (80.8)	−0.80 (12.32)	106 (84.8)	−6.02 (−9.27 to −2.77)	0.0003

continued

TABLE 11 Changes in clinical characteristics (*continued*)

Changes in clinical characteristics	Trial arm				Mean difference (95% CI)[a]	*p*-value[a]
	Spironolactone		Placebo			
	Mean (SD)	*n* (%)	Mean (SD)	*n* (%)		
Systolic blood pressure (mmHg)						
Baseline	129.16 (15.54)	125 (100)	130.06 (15.02)	124 (99.2)		
24 months	122.98 (18.21)	101 (80.8)	129.94 (16.07)	106 (84.8)		
Change from baseline to 24 months	−6.66 (19.75)	101 (80.8)	0.55 (17.01)	105 (84.0)	−7.22 (−12.27 to −2.16)	0.005
Diastolic blood pressure (mmHg)						
Baseline	75.72 (10.91)	125 (100)	75.59 (13.94)	124 (99.2)		
24 months	71.82 (11.06)	101 (80.8)	74.09 (11.54)	106 (84.8)		
Change from baseline to 24 months	−3.90 (12.21)	101 (80.8)	−1.32 (14.39)	105 (84.0)	−2.58 (−6.325 to 1.09)	0.17

a The mean differences between the spironolactone and the placebo groups, 95% CIs and the corresponding *p*-values were obtained using a two-sided *t*-test.

Note

The placebo group is the reference group.

Chapter 4 Discussion

The principal finding was that treatment with spironolactone does not improve either physical capacity or quality of life in this cohort of stable patients with permanent AF without systolic dysfunction. Given that there was no trend towards improvement in exercise tolerance or quality of life, it is unlikely that a larger study size would change the outcome if the same populations were studied.

It needs to be considered that the study aimed to be generalisable to the wider population of patients with AF. The inclusion criteria did not mandate evidence of HF and participants had a mean ejection fraction of 60%. In addition, the participants were not mandated to have echocardiographic evidence of diastolic dysfunction, as patients with AF have intrinsic diastolic dysfunction. As a result, the mean E/E′ ratio in the study patients was < 10, thus pointing towards the milder spectrum of diastolic dysfunction defined by echocardiographic parameters. Given the above considerations, it is possible that aldosterone receptor inhibition may still have potential in selected patients with advanced HFpEF or in unstable patients.

Atrial fibrillation has a prominent role in prognostication in HF. In the Candesartan in Heart failure–Assessment of Reduction in Mortality and morbidity (CHARM) programme, AF was associated with increased risk of death or hospitalisation for worsening HFpEF (hazard ratio 1.72).[6] Clinical trials of aldosterone antagonists [e.g. RALES, Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF)] uniformly show clinical benefit in systolic HF.[48–50] However, there is no established treatment for patients with AF with HFpEF. Currently there is no established treatment to improve HF-related outcomes in AF, and the IMPRESS-AF study has not improved the assessed outcomes in AF patients without systolic impairment.

Although there were numerically more cases of spontaneous return to sinus rhythm in the spironolactone group, such patients were few in both trial arms; the difference was not significant statistically and could therefore be a chance finding. Patients in the spironolactone group had one-third fewer hospitalisations for any reason, but the study was not powered to accurately assess this outcome. However, even if the difference was significant in a bigger study, use of spironolactone would be difficult to justify in view of its detrimental effects on renal function. Hospitalisations for cardiac cause were few in both trial groups, although the number of such cases was smaller in the spironolactone group.

Our findings generally agree with the results of the ALDO-DHF[21] and TOPCAT[22] trials, which did not demonstrate obvious clinical benefits of aldosterone antagonism in patients with HFpEF, mainly secondary to hypertension. In the IMPRESS-AF trial, positive effects were not found on any of the secondary outcomes despite a clear reduction in systolic blood pressure. This contrasts with clearly positive effects of the treatment in patients with systolic HF.

The study planning was based on expectations that spironolactone would improve exercise tolerance by inhibition and possible reversal of excessive cardiac fibrosis. According to a substudy of RALES, the improved survival in participants treated with spironolactone was linked to the ability of spironolactone to reduce serum markers of ongoing fibrosis (i.e. type I and III collagen synthesis).[34] In addition, aldosterone leads to cardiac invasion by proinflammatory mononuclear cells.[51] Aldosterone antagonists (i.e. spironolactone or eplerenone) ameliorate left ventricular fibrosis in animal models and reduce levels of serum markers of collagen turnover in humans with HFpEF ($n = 44$).[52,53] However, the antifibrotic effects of spironolactone seen in systolic HF did not translate into similar benefits in the IMPRESS-AF trial population.

Overall, spironolactone was well tolerated in according to its known profile of side effects and there were comparable rates of withdrawal from the study in the treatment and control trial groups. As expected, spironolactone reduced blood pressure, thus demonstrating adequate overall compliance with the drug as confirmed by the expected effect. However, there is a safety signal as there was a highly significant reduction of 6 ml/kg/1.73 m^2 in eGFR over 2 years of treatment. These data indicate potential harm from treating patients with AF with spironolactone and this needs to be considered and monitored if starting spironolactone in this population.

Limitations

The IMPRESS-AF trial did not mandate evidence of congestive HF and, given the need for exercise testing, it is possible that more fit patients were more likely to respond to the invitation. Although a large proportion of the study patients were recruited from primary care, improving generalisability of the results, patients unfamiliar with cycling were less likely to respond, which might have contributed to the higher proportion of male responders.

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 recognised questionnaires were used to assess quality of life, the tests were not specifically validated in patients with HFpEF.

Overall, 16% of participants did not complete the primary outcome tests and a proportion of patients did not adhere to the trial treatment, for example because of poor tolerance of the study drug. However, the study was powered to allow an estimated loss to follow-up of 20% of participants, and, therefore, the validity of the findings is likely to be maintained.

Recommendations for research

The trial did not have power to reliably define effects of spironolactone in patients with the most severe forms of HFpEF. However, given the significant detrimental effects of the drug in this trial population, further testing of spironolactone in patients with more advanced disease would be difficult to justify.

Chapter 5 Conclusions

Treatment of patients with AF and preserved ejection fraction with the aldosterone antagonist spironolactone does not improve exercise tolerance. The treatment also failed to improve quality of life and diastolic function in the tested population. Furthermore, spironolactone led to significant worsening of renal function, which may need to be considered if it is used in this patient population. The differences observed in the primary and key secondary outcomes reached neither statistical nor clinical significance and, since it was a well-powered trial, further RCTs of spironolactone in this patient population are not warranted.

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Contributions of authors

Eduard Shantsila (https://orcid.org/0000-0002-2429-6980) was involved in study design and data collection, wrote the first draft of the report and was involved in the editing of the manuscript.

Farhan Shahid (https://orcid.org/0000-0001-7635-5703) and was involved in data collection and editing of the manuscript.

Yongzhong Sun and **Jonathan J Deeks (https://orcid.org/0000-0002-8850-1971)** performed statistical analysis and edited the manuscript.

Ronnie Haynes (https://orcid.org/0000-0002-1935-1420) was involved in data collection and editing of the manuscript.

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Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Characteristics of those patients included in the primary analysis compared with those randomised

TABLE 12 Characteristics of those patients included in the primary analysis compared with those randomised

	Patients					
	All randomised			Only those who contributed to the primary outcome		
	Trial arm			Trial arm		
Baseline characteristics	Spironolactone ($N = 125$)	Placebo ($N = 125$)	Overall ($N = 250$)	Spironolactone ($N = 103$)	Placebo ($N = 106$)	Overall ($N = 209$)
Minimisation variables						
Peak VO_2 (ml/minute/kg)[a]						
≤ 16 ml, *n* (%)	77 (61.6)	78 (62.4)	155 (62.0)	60 (58.3)	63 (59.4)	123 (58.9)
> 16 ml, *n* (%)	48 (38.4)	47 (37.6)	95 (38.0)	43 (41.7)	43 (40.6)	86 (41.1)
Mean (SD)	14.5 (4.6)	14.6 (5.1)	14.5 (4.8)	14.9 (4.6)	15.1 (5)	15 (4.8)
Median (IQR)	13.9 (10.8–18.3)	14.4 (10.8–17.5)	14.1 (10.8–17.8)	14.5 (11.3–18.8)	14.6 (11.1–17.9)	14.5 (11.3–18.3)
Missing, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Demographic and other baseline variables						
Age (years)						
Mean (SD)	72.4 (7.1)	72.3 (7.9)	72.3 (7.4)	72.3 (7)	72.6 (7.3)	72.4 (7.2)
Median (IQR)	72.8 (68.3–77.2)	72.4 (67.4–77.6)	72.6 (67.6–77.6)	72.3 (67.6–77.1)	72.5 (67.6–77.6)	72.4 (67.6–77.1)
Missing, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
BMI (kg/m^2)						
Mean (SD)	30.4 (5.2)	30.5 (5.6)	30.5 (5.4)	30.2 (5.3)	30.4 (5.2)	30.3 (5.2)
Median (IQR)	29.1 (26.4–33.2)	30.1 (26.1–33.9)	29.7 (26.3–33.3)	29 (26.2–33.1)	30.1 (26.4–33.1)	29.6 (26.2–33.1)
Missing, *n* (%)	0 (0.0)	2 (1.6)	2 (0.8)	0 (0.0)	1 (0.9)	1 (0.5)
Sex, *n* (%)						
Female	28 (22.4)	31 (24.8)	59 (23.6)	20 (19.4)	26 (24.5)	46 (22)
Male	97 (77.6)	94 (75.2)	191 (76.4)	83 (80.6)	80 (75.5)	163 (78)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	Patients					
	All randomised			Only those who contributed to the primary outcome		
	Trial arm			Trial arm		
Baseline characteristics	Spironolactone (*N* = 125)	Placebo (*N* = 125)	Overall (*N* = 250)	Spironolactone (*N* = 103)	Placebo (*N* = 106)	Overall (*N* = 209)
Current medication, *n* (%)						
Yes	123 (98.4)	124 (99.2)	247 (98.8)	101 (98.1)	105 (99.1)	206 (98.6)
No	2 (1.6)	0 (0.0)	2 (0.8)	2 (1.9)	0 (0.0)	2 (1)
Missing	0 (0.0)	1 (0.8)	1 (0.4)	0 (0.0)	1 (0.9)	1 (0.5)
Smoking status, *n* (%)						
Current smoker	6 (4.8)	8 (6.4)	14 (5.6)	3 (2.9)	7 (6.6)	10 (4.8)
Ex-smoker	66 (52.8)	68 (54.4)	134 (53.6)	58 (56.3)	57 (53.8)	115 (55)
Non-smoker	53 (42.4)	49 (39.2)	102 (40.8)	42 (40.8)	42 (39.6)	84 (40.2)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Alcohol use (units per week)						
Mean (SD)	7.2 (9.9)	8.8 (10.8)	8.0 (10.4)	6.3 (8.6)	9.1 (11.3)	7.7 (10.1)
Median (IQR)	3.0 (0–12)	6.0 (0–14)	4.0 (0–13)	3 (0–10)	6 (0–14)	4 (0–12)
Missing, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
6MWT (metres)						
Mean (SD)	256.7 (83.4)	270.4 (89.5)	263.6 (86.6)	261.9 (80.6)	272.1 (85.3)	267.1 (83)
Median (IQR)	266.0 (196.0–316.0)	271.0 (200.0–330.0)	266.0 (200.0–322.0)	280 (210–320)	280 (208–336)	280 (210–322)
Missing, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Resting heart rate (b.p.m.)						
Mean (SD)	87.3 (19.4)	86.7 (18.7)	87.0 (19.0)	86 (18.6)	85.9 (19)	85.9 (18.7)
Median (IQR)	85.0 (74.0–99.0)	83.0 (74.0–97.0)	84.0 (74.0–97.0)	84 (74–98)	81 (73–94)	83 (74–95)
Missing, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

continued

TABLE 12 Characteristics of those patients included in the primary analysis compared with those randomised (*continued*)

	Patients					
	All randomised			Only those who contributed to the primary outcome		
	Trial arm			Trial arm		
Baseline characteristics	Spironolactone (*N* = 125)	Placebo (*N* = 125)	Overall (*N* = 250)	Spironolactone (*N* = 103)	Placebo (*N* = 106)	Overall (*N* = 209)
Peak heart rate during CPET (b.p.m.)						
Mean (SD)	128.4 (26.1)	129.9 (25.4)	129.1 (25.7)	128.7 (26.4)	131.8 (25.5)	130.3 (25.9)
Median (IQR)	129.0 (109.0–150.0)	126.0 (112.0–148.0)	127.0 (110.0–149.0)	129 (109–150)	130.5 (114–150)	129 (113–150)
Missing, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity, *n* (%)						
White	118 (94.4)	118 (94.4)	236 (94.4)	97 (94.2)	101 (95.3)	198 (94.7)
Mixed	1 (0.8)	0 (0.0)	1 (0.4)	3 (2.9)	2 (1.9)	5 (2.4)
Black	3 (2.4)	3 (2.4)	6 (2.4)	3 (2.9)	1 (0.9)	4 (1.9)
Asian	3 (2.4)	2 (1.6)	5 (2.0)	0 (0.0)	2 (1.9)	2 (1)
Other ethnic group	0 (0.0)	2 (1.6)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	97 (94.2)	101 (95.3)	198 (94.7)
BNP concentration (pg/ml)						
Mean (SD)	163.5 (125.4)	183.3 (168.5)	173.4 (148.5)	160 (130.6)	181.5 (172.5)	170.9 (153.2)
Median (IQR)	122.0 (73.0–230.0)	136.0 (81.7–241.0)	127.0 (77.9–236.0)	117 (69–228)	132 (81.4–241)	119 (74.3–229)
Missing, *n* (%)	0 (0.0)	1 (0.8)	1 (0.4)	0 (0.0)	1 (0.9)	1 (0.5)
Systolic blood pressure (mmHg)						
Mean (SD)	129.2 (15.5)	130.1 (15.0)	129.6 (15.3)	128.7 (15.4)	129.8 (14.8)	129.3 (15.1)
Median (IQR)	130.0 (117.0–140.0)	129.0 (118.0–142.0)	129.0 (117.0–140.0)	129 (117–140)	129 (118–142)	129 (118–140)
Missing, *n* (%)	0 (0.0)	1 (0.8)	1 (0.4)	0 (0.0)	1 (0.9)	1 (0.5)

	Patients					
	All randomised			Only those who contributed to the primary outcome		
	Trial arm			Trial arm		
Baseline characteristics	Spironolactone (*N* = 125)	Placebo (*N* = 125)	Overall (*N* = 250)	Spironolactone (*N* = 103)	Placebo (*N* = 106)	Overall (*N* = 209)
Diastolic blood pressure (mmHg)						
Mean (SD)	75.7 (10.9)	75.6 (13.9)	75.7 (12.5)	75.4 (11)	75.5 (14.7)	75.4 (13)
Median (IQR)	75.0 (67.0–83.0)	74.0 (68.0–82.0)	74.0 (68.0–82.0)	74 (67–82)	73 (67–82)	73.5 (67–82)
Missing, *n* (%)	0 (0.0)	1 (0.8)	1 (0.4)	0 (0.0)	1 (0.9)	1 (0.5)
Waist circumference (cm)						
Mean (SD)	99.5 (12.5)	100.3 (14.4)	99.9 (13.5)	98.8 (12.4)	99.3 (13)	99.1 (12.6)
Median (IQR)	99.0 (91.4–106.7)	101.0 (91.0–106.7)	99.1 (91.4–106.7)	96.5 (91–106)	100 (91.2–106.3)	99 (91–106)
Missing, *n* (%)	0 (0.0)	2 (1.6)	2 (0.8)	0 (0.0)	2 (1.9)	2 (1.0)
Hip circumference (cm)						
Mean (SD)	107.4 (10.0)	108.0 (13.2)	107.7 (11.7)	107 (10.1)	107.3 (12.7)	107.1 (11.5)
Median (IQR)	106.7 (101.0–112.0)	106.7 (100.0–114.3)	106.7 (100.0–114.3)	106 (99.1–111.8)	106.7 (100–114.3)	106.7 (100–114.3)
Missing, *n* (%)	0 (0.0)	2 (1.6)	2 (0.8)	0 (0.0)	2 (1.9)	2 (1.0)
Left ventricular ejection fraction (%)						
Mean (SD)	60.4 (5.4)	60.5 (5.7)	60.5 (5.5)	60 (5.2)	61 (5.9)	60.5 (5.6)
Median (IQR)	58.0 (56.6–62.0)	58.0 (56.3–63.0)	58.0 (56.4–63.0)	58 (56.4–61.5)	59 (56.8–64)	58 (56.6–62.9)
Missing, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mitral valve measurement: E/E′ ratio						
Mean (SD)	10.7 (4.4)	10.6 (4.2)	10.7 (4.3)	10.3 (3.9)	10.6 (4.1)	10.5 (4)
Median (IQR)	9.8 (8.0–12.0)	9.7 (7.5–13.0)	9.8 (7.8–12.6)	9.8 (7.9–11.9)	9.6 (7.5–13)	9.6 (7.7–12.6)
Missing, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

continued

TABLE 12 Characteristics of those patients included in the primary analysis compared with those randomised (*continued*)

	Patients					
	All randomised			Only those who contributed to the primary outcome		
	Trial arm			Trial arm		
Baseline characteristics	Spironolactone (*N* = 125)	Placebo (*N* = 125)	Overall (*N* = 250)	Spironolactone (*N* = 103)	Placebo (*N* = 106)	Overall (*N* = 209)
EQ-5D-5L score						
Mean (SD)	0.8 (0.2)	0.8 (0.2)	0.8 (0.2)	0.8 (0.2)	0.8 (0.1)	0.8 (0.2)
Median (IQR)	0.8 (0.7–0.9)	0.9 (0.7–0.9)	0.9 (0.7–0.9)	0.9 (0.8–0.9)	0.9 (0.8–0.9)	0.9 (0.8–0.9)
Missing, *n* (%)	4 (3.2)	5 (4.0)	9 (3.6)	3 (2.9)	3 (2.8)	6 (2.9)
MLWHF score[b]						
Mean (SD)	22.9 (20.4)	21.9 (22.9)	22.4 (21.7)	22.1 (20.7)	19.3 (20.7)	20.7 (20.7)
Median (IQR)	17.0 (6.3–35.8)	14.0 (5.8–30.0)	14.0 (6.0–33.8)	14 (6–35)	11.5 (5–25.7)	12 (6–31)
Missing, *n* (%)	8 (6.4)	4 (3.2)	12 (4.8)	6 (5.8)	4 (3.8)	10 (4.8)

b.p.m., beats per minute; CPET, cardiopulmonary exercise test; IQR, interquartile range.

a The dichotomised peak VO_2 score (ml/minute/kg) was used as the minimisation variable.

b To score the MLWHF questionnaire, at most 20% of the 21 responses were allowed to be missing, which was equivalent to four data items. If there were ≤ 4 data items missing, then mean substitution was used to impute the missing responses. The questionnaire was scored by summating the responses to all 21 questions; otherwise, the person's score was left missing.

Appendix 2 Histograms of compliance with treatment allocation

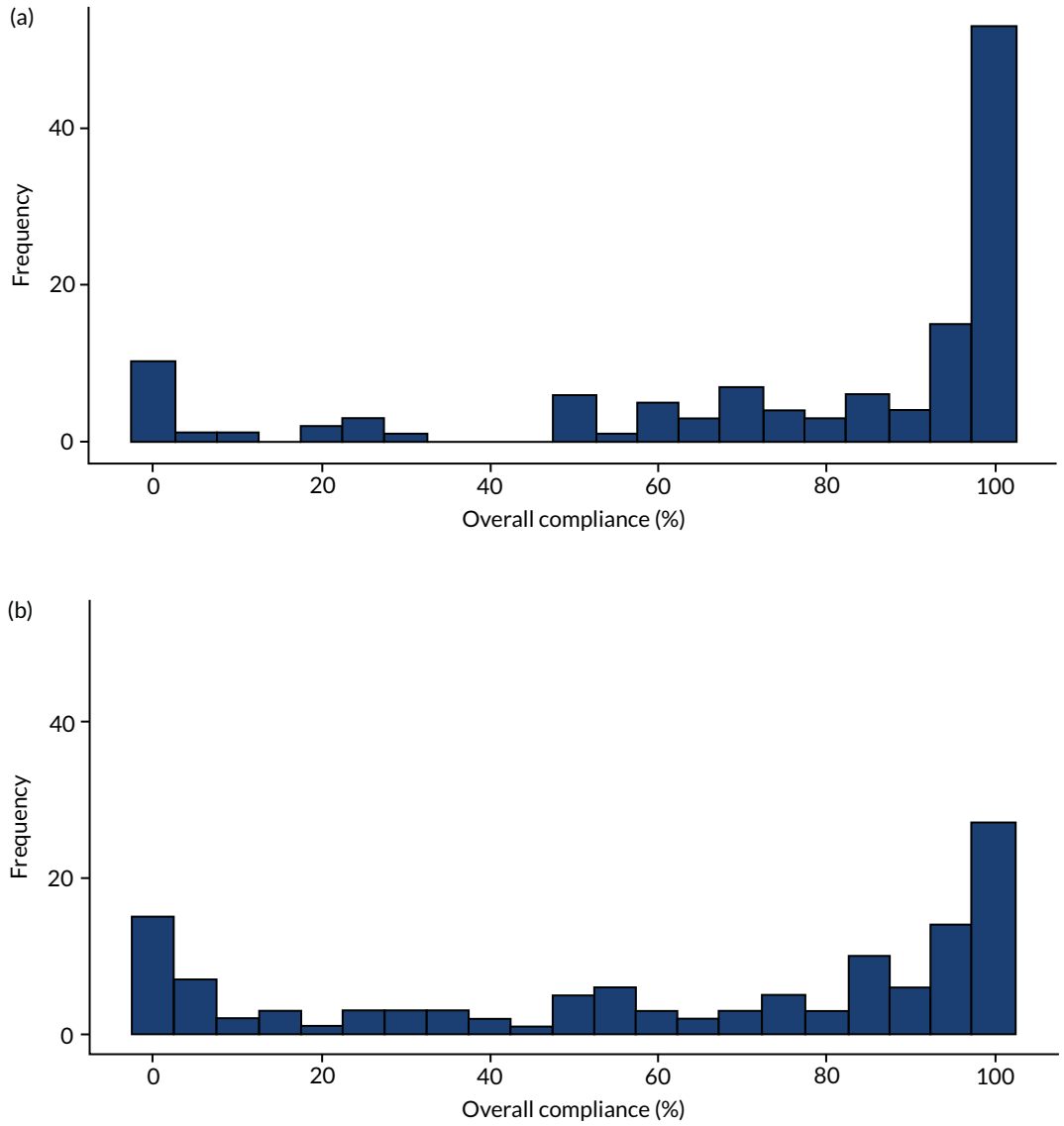

FIGURE 3 Histogram of compliance with treatment allocation by trial arms. (a) Placebo; and (b) spironolactone. Compliance with treatment was defined as ≥ 80% of capsules taken across the full 24-month trial duration or to time of death.

Appendix 3 Protocol deviations by trial arm

TABLE 13 Protocol deviations

Protocol deviation	Trial arm (*n*)	
	Spironolactone (*N* = 31)	Placebo (*N* = 19)
Trial procedure/activity schedules not adhered to	5	5
Data management[a]	7	3
SAE not reported in correct time frame[b]	0	4
Trial medication reported with incorrect drug quantity	2	0
SAE assessment outside time frame, i.e. ≥ 7 days[c]	1	3
Raised levels of potassium follow-up procedure not adhered to	14	4
Participant prescribed spironolactone and taking trial medication	2	0

SAE, serious adverse event.
a Duplicate identification numbers used, incorrect identification numbers used on cardiopulmonary exercise test reports and incorrect identification numbers used on case report forms.
b Reported > 7 days after site became aware of the SAE.
c Causality assessment > 7 days after SAE form was completed.

EME
HS&DR
HTA
PGfAR
PHR

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