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

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Scientific summary

The IMPRESS-AF RCT

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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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