PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	IMproved exercise tolerance in patients with PReserved Ejection fraction by Spironolactone on myocardial fibrosiS in Atrial Fibrillation Rationale and design of the IMPRESS-AF randomized controlled trial
AUTHORS	Shantsila, Eduard; Haynes, Ronnie; Calvert, Melanie; Fisher, James; Kirchhof, Paulus; Gill, Paramjit; Lip, Gregory

VERSION 1 - REVIEW

REVIEWER	Hidekatsu Fukuta Nagoya City University Graduate School of Medical Sciences Nagoya, Japan
REVIEW RETURNED	04-May-2016

GENERAL COMMENTS	This trial was designed to examine whether, treatment with spironolactone as compared to placebo improves exercise tolerance, quality of life and diastolic function in heart failure (HF) patients with preserved ejection fraction (EF) and permanent atrial fibrillation (AF). Major comments. EF>55% was used for the inclusion criteria in this trial. However, it is important to recognize that patients with HF with preserve EF (HFpEF) and those with recovered EF have distinct clinical phenotypes and prognosis (Basuray A et al. Heart failure with recovered ejection fraction: clinical description, biomarkers, and outcomes. Circulation. 2014;129:2380–2387.) Thus, patients with HF with recovered EF should be removed in this trial. This trial used E/e' as a marker of diastolic function. The authors should mention the validity of using E/e' as a marker of diastolic function in permanent AF patients citing the relevant articles. EF during AF varies depending on the preceding cardiac cycle lengths. The authors should show how to determine EF. Do they calculate EF as a mean of several consecutive cardiac cycles? This issue is also the case in calculating E/e'. The sample size was calculated to detect a difference of 2 ml/min/kg in peak VO2. The authors should explain whether improvement of 2 ml/min/kg in peak VO2 is clinically meaningful in HFpEF patients. Minor comments.

	Ref.49 reported the effect of mineralocorticoid receptor antagonism on diastolic function and myocardial fibrosis in idiopathic dilated cardiomyopathy patients with EF<45%. Thus, ref.49 should be replaced with another relevant article.

REVIEWER	Kevin Vernooy Maastricht University Medical Center the Netherlands
REVIEW RETURNED	23-May-2016

GENERAL COMMENTS	The authors have submitted the proposal of new study on a very interesting topic. The aim of the study is to evaluate whether spironolactone use in patients with preserved ejection and permanent atrial fibrillation will improve exercise tolerance. There are some issues I would like to address. - Why was VO2 max choosen as a primary endpoint, since this tests has it limitations in a group of patients that are probably of higher age. Why wasn't 6MHWT choosen? - A lot of patients need te be recruited; are the authors really convinced that this study can be performed as a single center study. Moreover, many patients that are potential candidates for this study are not seen by a cardiologist but by their GP en therefore will be harder to find. - Since permanent atrial fibrillation is the inclusion criterium I would suggest to use class I and class III (with the exception of amiodarone) as an exclusion criterium. - Since hypertension is major cause of AF, it should be stated that hypertension should be treated before treatment with spironolactone - Many patients with permanent AF have a slightly diminished ejection fraction due to the irregular rhythm; why was the LVEF>55% choosen, thereby potentially "missing" many potential candidates. Why wasn't 50% choosen? - The power calculation was performed on improved VO2max in a study group that underwent physical training; can this really be translated to this trial; isn't there a potential underpower?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Hidekatsu Fukuta
Institution and Country: Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

This trial was designed to examine whether, treatment with spironolactone as compared to placebo improves exercise tolerance, quality of life and diastolic function in heart failure (HF) patients with preserved ejection fraction (EF) and permanent atrial fibrillation (AF).

Major comments.

Comment: EF>55% was used for the inclusion criteria in this trial. However, it is important to recognize that patients with HF with preserve EF (HFpEF) and those with recovered EF have distinct clinical phenotypes and prognosis (Basuray A et al. Heart failure with recovered ejection fraction: clinical description, biomarkers, and outcomes. Circulation. 2014;129:2380–2387.) Thus, patients with HF with recovered EF should be removed in this trial.

>>> Response: Thank you for the comment. We do appreciate that patients with recovered systolic LV impairment (HF-Recovered in the study by Basuray et al.) have a better outcome. In the study by Basuray et al. HF-Recovered patients were more likely to have non-ischemic cardiomyopathy, thus this group probably included more patients that had recovered from myocarditis, a condition known to be relatively benign. Only a minority of patients with HF-Recovered had AF, and even fewer would have permanent AF (not specified in the paper). An overlap between the Basuray et al. population with that of the IMPRESS-AF population is probably made even lower by our stricter definition of normal EF (>55% as opposed to >50% in the Basuray et al. study). We are unaware of any patients with HF-Recovered in the IMPRESS-AF population.

Comment: This trial used E/e' as a marker of diastolic function. The authors should mention the validity of using E/e' as a marker of diastolic function in permanent AF patients citing the relevant articles.

>>> Response: Thank you for pointing this out. References to the following papers supporting utility of E/e' in AF have been added:

Sohn DW, Song JM, Zo JH, et al. Mitral annulus velocity in the evaluation of left ventricular diastolic function in atrial fibrillation. Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography 1999;12(11):927-31.

Kusunose K, Yamada H, Nishio S, et al. Clinical utility of single-beat E/e' obtained by simultaneous recording of flow and tissue Doppler velocities in atrial fibrillation with preserved systolic function. JACC Cardiovasc Imaging 2009;2(10):1147-56.

Aljaroudi W, Alraies MC, Halley C, et al. Impact of progression of diastolic dysfunction on mortality in patients with normal ejection fraction. Circulation 2012;125(6):782-8.

Nagueh SF, Kopelen HA, Quinones MA. Assessment of left ventricular filling pressures by Doppler in the presence of atrial fibrillation. Circulation 1996;94(9):2138-45.

Temporelli PL, Scapellato F, Corra U, et al. Estimation of pulmonary wedge pressure by transmitral Doppler in patients with chronic heart failure and atrial fibrillation. The American journal of cardiology 1999;83(5):724-7.

Chirillo F, Brunazzi MC, Barbiero M, et al. Estimating mean pulmonary wedge pressure in patients with chronic atrial fibrillation from transthoracic Doppler indexes of mitral and pulmonary venous flow velocity. Journal of the American College of Cardiology 1997;30(1):19-26.

Also we included a reference to the latest Recommendations for the evaluation of left ventricular diastolic function by echocardiography:

Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography 2016;29(4):277-314.

Comment: EF during AF varies depending on the preceding cardiac cycle lengths. The authors should show how to determine EF. Do they calculate EF as a mean of several consecutive cardiac cycles? This issue is also the case in calculating E/e'.

>>> Response: Thank you for pointing this out. The study protocol specifies that average values from 10 consecutive cardiac cycles will be calculated to obtain EF and E/e'. This information has now been added to the Design section of the manuscript.

Comment: The sample size was calculated to detect a difference of 2 ml/min/kg in peak VO2. The authors should explain whether improvement of 2 ml/min/kg in peak VO2 is clinically meaningful in HFpEF patients.

>>> Response: Thank you for the comment. An improvement of two ml/min/kg in peak VO2 in HF is undoubtedly clinically relevant in HFpHF. For example, in a recent study multivariable regression analysis showed that reduction in 1 ml/min/kg of peak VO2 was associated with highly significant increase in a composite outcome of all-cause mortality or cardiac transplant (hazard ratio 0.86, 95% confidence interval 0.79-0.94, p<0.001). A similar difference in peak VO2 was factored for the design of the recent Aldo-DHF study of spironolactone in patients with HFpEF, 95% of whom were free from AF.

The following text has been added: 'Published data in HFpEF suggest that such a difference would be clinically relevant and it was factored for the design of the recent Aldo-DHF study of spironolactone in patients with HFpEF, 95% of whom were free from AF.[References]'

Minor comments.

Comment: Ref.49 reported the effect of mineralocorticoid receptor antagonism on diastolic function and myocardial fibrosis in idiopathic dilated cardiomyopathy patients with EF<45%. Thus, ref.49 should be replaced with another relevant article.

>>> Response: Thank you for pointing the error out. HFrEF was meant rather than HFpEF; this has now been corrected. The reference is correct and we are not aware of similar data for HFpEF.

Reviewer: 2
Reviewer Name: Kevin Vernooy
Institution and Country: Maastricht University Medical Center, the Netherlands

The authors have submitted the proposal of new study on a very interesting topic. The aim of the study is to evaluate whether spironolactone use in patients with preserved ejection and permanent atrial fibrillation will improve exercise tolerance.

Comment: There are some issues I would like to address.
- Why was VO2 max choosen as a primary endpoint, since this tests has it limitations in a group of patients that are probably of higher age. Why wasn't 6MHWT choosen?

>>> Response: Thank you for the comment. Given that the main objective of the study was to establish the effect of spironolactone on heart failure progression we wanted to have a reproducible and robust assessment of exercise tolerance, thus, the choice of peak VO2 which is a well-established measure of HF functional status. We agree that this test may have limitations in some older people (e.g., due to arthritis) and therefore this was part of the exclusion criteria ('Any participant characteristic that may interfere with adherence to the trial protocol'). In all cases, we aim to obtain high-quality peak VO2 data. We additionally included 6MWT to have a measure relevant to the patient's daily activity (i.e., walking), which would provide more meaningful and easily interpretable data to many healthcare providers, as opposed to more technical CPET data.

Comment: - A lot of patients need te be recruited; are the authors really convinced that this study can

be performed as a single center study. Moreover, many patients that are potential candidates for this study are not seen by a cardiologist but by their GP en therefore will be harder to find.

>>> Response: Thank you for the comment. Indeed, we had expected recruitment to be challenging and included provision for recruitment from both primary care (GP practices) and secondary care (hospital clinics). Using this strategy recruitment has been successfully undertaken in accordance with the planned pace (250 target patients had been recruited by 21/06/2016).

Comment: - Since permanent atrial fibrillation is the inclusion criterium I would suggest to use class I and class III (with the exception of amiodarone) as an exclusion criterium.

>>> Response: All IMPRESS-AF patients have permanent AF and are managed following rate control strategy. The above agents are contraindicated in the study population according to the current guidelines. For this reason the study protocol does not specify them in the exclusion criteria list.

Comment: - Since hypertension is major cause of AF, it should be stated that hypertension should be treated before treatment with spironolactone

>>> Response: Thank you. The following information has been specified in the Study design section: 'In patients with hypertension antihypertensive treatment will was established before the recruitment and patients with systolic blood pressure more 160 mmHg were excluded.'

Comment: - Many patients with permanent AF have a slightly diminished ejection fraction due to the irregular rhythm; why was the LVEF>55% choosen, thereby potentially "missing" many potential candidates. Why wasn't 50% choosen?

>>> Response: Thank you for the comment. The cutoff was chosen based on the recommended values for the normal LVEF at the time of the study design (Lang RM, et al. Recommendations for chamber quantification. Eur J Echo. 2006;7(2):79-108.). The reference has now been added to the manuscript.

Comment: - The power calculation was performed on improved VO2max in a study group that underwent physical training; can this really be translated to this trial; isn't there a potential underpower?

>>> Response: Thank you for the comment. At the time of the study design (2011-2012) there was little data to advise on the magnitude of VO2 max improvement elicited by treatments in HFpEF. The study used as a reference point for the power calculation indicated a minimum of 200 patients to be recruited. To help ensure adequate power a decision was made to increase the number by 25% (i.e., n=250)

VERSION 2 – REVIEW

REVIEWER	Hidekatsu Fukuta, MD, PhD Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan
REVIEW RETURNED	15-Jul-2016

GENERAL COMMENTS	The authors adequately responded to the reviewer's major comments. However, they did not respond to the reviewer's minor comment. On the revised manuscript, they still use the term HFpEF, which should

	be replaced with HFrEF.