Synopsis of the Clinical Trial Report

ALDOSTERONE RECEPTOR BLOCKADE IN DIASTOLIC HEART FAILURE

A double-blind, randomised, placebo-controlled, parallel group study to determine the effects of spironolactone on exercise capacity and diastolic function in patients with symptomatic diastolic heart failure

Aldo-DHF

investigational product:	Verosiron T (Spironolactone 25 mg)
Indication:	Diastolic Heart Failure
Phase of the clinical trial:	IIb
EudraCT-No:	2006-002605-31
Trial Registration:	ISRCTN94726526 (http://www.controlled-trials.com)

Coordinating investigator: **Prof. Dr. med. Burkert Pieske**
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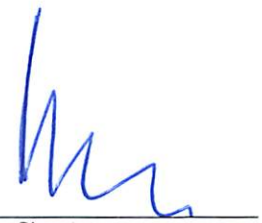
Prof. Dr. Dr. Götz Gelbrich
Institute for Clinical Epidemiology and Biometry (ICE-B)
University of Würzburg, Josef-Schneider-Str. 2, 97080 Würzburg, Germany

Start of clinical trial:	30.03.2007
End of clinical trial:	22.05.2012

Report Signatures

Confirmation of the Final Report

We hereby certify that we agree with the content of this final report: this clinical trial was performed according to the Declaration of Helsinki, the guidelines for Good Clinical Practice (GCP), as well as all pertinent national laws.

Authorized representative of the sponsor and coordinating investigator: Prof. Dr. med. Burkert Pieske	16.8.13 Date	 Signature
Coordinating investigator PD Dr. Frank Edelmann	Date	Signature
Biometrician: Prof. Dr. Dr. Götz Gelbrich	Date	Signature

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Authorized representative of the sponsor and coordinating investigator:

Prof. Dr. med. Burkert Pieske

Date Signature

Coordinating investigator
PD Dr. Frank Edelmann

16. August 2013

Date Signature

Biometrician:
Prof. Dr. Dr. Götz Gelbrich

Date Signature

Report Signatures

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Authorized representative of the sponsor and coordinating investigator:		
Prof. Dr. med. Burkert Pieske	Date	Signature
Coordinating investigator		
PD Dr. Frank Edelmann	Date	Signature
Biometrician:		
Prof. Dr. Dr. Götz Gelbrich	27-AUG-2013 Date	Signature

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1 Title of study

ALDOSTERONE RECEPTOR BLOCKADE IN DIASTOLIC HEART FAILURE

A double-blind, randomised, placebo-controlled, parallel group study to determine the effects of spironolactone on exercise capacity and diastolic function in patients with symptomatic diastolic heart failure

This report contains the final version of the trial protocol including Amendment 1 to 3. An overview of the contents of the individual amendments can be found in the appendix (19.2).

2 Study type

Aldo-DHF was a multicenter, randomized, placebo-controlled, double-blind, two-armed, parallel-group study according to the German drug law (AMG).

3 Sponsor and authorized representative of the sponsor

Name: Georg-August-Universität Göttingen, Bereich Humanmedizin

Authorized representative of the sponsor: Prof. Dr. med. Burkert Pieske

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4 Coordinating investigator

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Email : pieske@med.uni-goettingen.de

5 Trial sites and principal investigators

Patients were enrolled from 10 trial sites in Germany and Austria. The following table showes the sites, the principle investigator and the number of recruited patients.

Trial site	Principle Investigator	Number of patients recruited
Georg-August-Universität Göttingen, Abt. für Kardiologie und Pneumologie, Robert-Koch-Str. 40, 37075 Göttingen	Prof. Dr. med. B. Pieske	316
Universität Graz, Univ.-Klinik für Innere Medizin, Klinische Kardiologie; Auenbruggerplatz 15, 8036 Graz	Dr. med. A. Schmidt	68
Reha-Zentrum Spreewald, Innere Medizin und Konservative Orthopädie; Zur Spreewaldklinik 14, 03096 Burg (Spreewald)	Dr. med. W. Kamke	12
Charité–Campus Benjamin Franklin, Medizinische Klinik II – Kardiologie und Pulmologie; Hindenburgdamm 30, 12207 Berlin	Prof. Dr. med. C. Tschöpe	6

Trial site	Principle Investigator	Number of patients recruited
Charité Campus Virchow-Klinikum, Medizinische Klinik mit Schwerpunkt Kardiologie; Augustenburger Platz 1, 13353 Berlin	Dr. med. H.-D. Düngen	6
Universität Leipzig, Herzzentrum, Klinik für Innere Medizin/Kardiologie; Strümpellstr. 39, 04289 Leipzig	PD Dr. med. S. Gielen	5
Otto-von-Guericke-Universität Magdeburg, Klinik für Kardiologie, Pneumologie und Angiologie; Leipziger Str. 44, 39120 Magdeburg,	PD Dr. med. A. Schmeisser	4
Herzinsuffizienzambulanz, Deutsches Zentrum für Herzinsuffizienz ● Würzburg, Universitätsklinik Würzburg, Straubmühlweg 2a, Haus A9, 97078 Würzburg	Prof. Dr. med. C. Angermann	3
Klinikum Augsburg, I. Medizinische Klinik Stenglinstr. 2, 86156 Augsburg	Prof. Dr. med. W. von Scheidt	2
Universitätsklinikum Essen, Abteilung für Kardiologie Hufelandstr. 55, 45122 Essen	Prof. Dr. med. T. Neumann	1
Klinikum Augsburg, I. Medizinische Klinik, Stenglinstr. 2, 86156 Augsburg	Prof. Dr. med. W. von Scheidt	0
Universitäres Herzzentrum Hamburg gGmbH, Klinik für Herz- u. Gefäßchirurgie, Martinistr. 52, 20246 Hamburg	Prof. Dr. med. A. Costard-Jäckle	0
Universitätsklinikum des Saarlandes, Klinik für Innere Medizin III, Kirrbergstraße, 66421 Homburg/ Saar	Prof. Dr. med. M. Böhm	0

6 Publication of the clinical trial

The trial was be registered at the online-register www.controlled-trials.com and has the register-No ISRCTN94726526.

Edelmann F, Wachter R, Schmidt AG, Kraigher-Krainer E, Colantonio C, Kamke W, Duvinage A, Stahrenberg R, Durstewitz K, Löffler M, Düngen HD, Tschöpe C, Herrmann-Lingen C, Halle M, Hasenfuss G, Gelbrich G, Pieske B; Aldo-DHF Investigators.
Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial.
JAMA. 2013 Feb 27;309(8):781-91.

Edelmann F, Schmidt AG, Gelbrich G, Binder L, Herrmann-Lingen C, Halle M, Hasenfuss G, Wachter R, Pieske B.
Rationale and design of the 'aldosterone receptor blockade in diastolic heart failure' trial: a double-blind, randomized, placebo-controlled, parallel group study to determine the effects of spironolactone on exercise capacity and diastolic function in patients with symptomatic diastolic heart failure (Aldo-DHF).
Eur J Heart Fail. 2010 Aug;12(8):874-82.

7 Trial duration

The Aldo-DHF study started on 30.03.2006 which was equal to the „First Patient In“ (FPI) date. The last patient was recruited on 15.04.2011. „Last Patient Out“ (LPO) was the last safety visit (12 months + 4 weeks) on 22.05.2012.

8 Objectives of the trial

The primary objective of Aldo-DHF was to determine whether spironolactone is superior to placebo in improving diastolic function and maximal exercise capacity in subjects with HF with preserved EF (i.e. diastolic heart failure).

Secondary objectives of this study are to determine in subjects with diastolic heart failure whether spironolactone is superior to placebo in improving several other measures of exercise capacity and diastolic function, as well as quality of life, neuroendocrine activation, morbidity and mortality. The study will also investigate clinical safety aspects.

9 End points of the clinical trial

Primary end point:

There will be two primary endpoints:

- Change of peak VO_2 from baseline to 12-months follow-up
- Change of E/E' from baseline to 12-months follow-up

Major secondary end points

- Change in primary endpoints at 18 months
- Change in echocardiographic Grade of diastolic dysfunction
- Change in neuroendocrine activation (natriuretic peptides)
- Change in 6-minutes walking distance
- Change in quality of life (Minnesota living with heart failure questionnaire; SF 36)
- Combined and separately morbidity and mortality (all-cause, cardiovascular)

Accompanied secondary end points

- Change in echocardiographic parameters of diastolic dysfunction (E/A, EDT, IVRT, S/D, AR, V_p, $PVAR_{dur}$, A_{dur}, Tei-Index, LV mass, LA area)
- Change in anaerobic threshold (spiroergometry), change in V_E/VCO_2 slope (ventilatory efficiency)
- Change of Borg score of breathlessness
- Change in patient global assessment on 7-point scale

Safety end points

- Clinical tolerablitiy of study medication

10 Clinical trial design / methodology

Aldo-DHF is a mulicentre, randomized, placebo-controlled, double-blind, two-armed, parallel group study. Participating trial sites will screen all consecutive outpatients and inpatients that fulfill the pre-screening criteria, i. e. signs and symptoms of heart failure and a LVEF≥50%.

Eligible patients were randomly assigned to receive either spironolactone (25mg/d) or matching placebo. The randomisation ratio was 1:1 for either spironolactone or placebo using Pocock's minimization algorithm. Randomisation was stratified by grade of diastolic dysfunction (I versus II+III), rhythm (sinus versus other) and center. The allocation sequence was implemented remotely via internet/ telefax by the Clinical Trials Centre Leipzig (University of Leipzig, Germany).

The first dose of study drug was administered immediately after randomisation under the supervision of the local investigator. No further up-titration was planned. Patients were followed on blinded study medication for 12 months plus an additional safety period of 4 weeks after termination of individual study-related therapy.

11 Total number of patients

Of 795 patients screened from March 2007 to April 2011, 422 were included and randomized to receive spironolactone (n=213) or placebo (n=209); 400 were included in the primary analysis. For an overview see Consort Flow Chart presented at the end of this report.

Randomisation was done in stratified manner according to the prepared scheme of randomisation. No randomisation failure occurred.

12 Inclusion criteria

Patients must meet ALL of the following criteria:

- Current heart failure symptoms consistent with NYHA II or beyond
- Left ventricular ejection fraction (LVEF) ≥ 50% at rest
- Sinus rhythm or atrial fibrillation
- if sinus rhythm echocardiographic parameters of diastolic dysfunction (Grade ≥ I)
- Peak VO_2 ≤ 25 ml/kg/min
- Males and females of age ≥ 50 years
- Written informed consent of the patient

13 Exclusion criteria

Patients will be excluded for ANY ONE of the following reasons:

- definite or probable pulmonary disease (VC<80% or FEV1<80% of reference values on spirometry)
- severe obesity (BMI ≥ 36 kg/m^2)
- psychological disorders with suspected interaction to study outcome
- Prior documented intolerance to an aldosterone receptor antagonist
- Prior documented systolic heart failure (LVEF ≤ 40%)
- Changes in concomitant medication within the last two weeks prior screening visit
- Significant coronary artery disease (current angina pectoris or ischemia on stress tests; untreated coronary stenosis >50%; Myocardial infarction or CABG within the last 3 months)
- Known contraindications for spironolactone
- Significant laboratory abnormalities (potassium ≥ 5.1 mmol/L; hemoglobin ≤ 11g/dL, hematocrit ≤ 33%)
- Significant renal dysfunction (creatinine > 1.8 mg/dL or eGFR < 30ml/min/1,73m²)
- Concomitant therapy with a potassium-sparing diuretic (e.g., triamterene, amiloride), potassium substitution, or high-dose acetylsalicylic acid (>500 mg/d) or permanent intake of non-steroidal antiphlogistic agents, digitalis
- Insulin-dependent diabetes mellitus with a history of ketoacidosis
- Suspected metabolic acidosis
- Significant hypotension (blood pressure < 90 mmHg systolic and/or <50 mmHg diastolic)
- Any patient characteristic that may interfere with compliance with the study protocol, such as dementia, substance abuse, history of non-compliance with prescribed medications or medical appointments
- Pregnant or nursing women

- Women with child bearing potency without effective contraception (except for implants, injectables, combined oral contraceptives, some IUDs or vasectomised partner)
- Concomitant participation in other clinical trials
- Therapy with an aldosterone receptor antagonist within the last 3 months
- Participation in another clinical trial within the last 30 days

14 Investigational Product

Double-blind study drug will consist of spironolactone (Verospiron T) 25 mg or placebo and is orally applied as tablet.

Production of spironolactone will be done by HORMOSAN PHARMA AG and of identical matching placebo in cooperation by Allphamed PHARBIL. Packaging, labelling and storage of study drug (spironolactone, matching placebo) will be done by Allphamed PHARBIL.

15 Duration of treatment and trial procedures

Patients were followed on blinded study medication for 12 months plus an additional safety period of 4 weeks after termination of individual study-related therapy (interim visits at 1 week and 3, 6, and 9 months). Additionally, the blindet follow-up of patients recruites in the first 6 months will last for up to 18 months.

At baseline and the 6 and 12 month follow-up visits, all patients underwent physical examination, echocardiography, cardiopulmonary exercise testing (CPET), six-minute walk testing (6MWT), quality of life (QoL) assessment, and blood sampling. QoL was assessed by the 36-Item Short Form Health Survey (SF-36), the Minnesota Living With Heart Failure Questionnaire (MLWHFQ), and the Hospital Anxiety and Depression Scale (HADS).

16 Statistical methods / criteria for evaluation

16.1 Primary endpoint

Analyses of the primary endpoints were carried out by two-sided Mann-Whitney U tests at a type I error level of 0.025 (adjustment for two primary tests). A patient who died was assigned the worst rank in both tests, reflecting the worst case of functional loss. A missing value in one of the endpoints did not preclude analysis of the other. The quantitative effects of the intervention were assessed by analysis of covariance (ANCOVA) with the follow-up value as the dependent variable, treatment as a factor, and the baseline value as the covariate. All analyses were based on the intent to treat principle.

IBM SPSS version 20 was used as statistical software.

16.2 Secondary endpoint

Pre-specified secondary endpoints were changes in anaerobic threshold, VE/VCO_2 slope and Borg dyspnea scale during CPET, E and e' velocities, grade of diastolic dysfunction, left ventricular mass index and left atrial volume index from echocardiography, six-minute-walk-distance, NT-proBNP, and the patient reported MLWHFQ total score, SF-36 Physical Functioning scale and symptoms of depression measured by the PHQ-9 sum score. Changes in all other variables, including changes in baseline characteristics, were analyzed in an exploratory manner. No adjustments for multiple comparisons were planned, except for the primary endpoint. Analyses were carried out by ANCOVA, binary or ordinal logistic regression with the follow-up value as the dependent variable, treatment as a factor, and the baseline value as the continuous or categorical covariate, as appropriate for quantitative, binary or ordinal categorical variables. Between group comparisons are presented as mean differences or odds ratios. NT-proBNP was analyzed on the logarithmic scale, and the result was transformed back by the exponential function, leading to a geometric mean ratio instead of a mean difference.

16.3 Safety analyses

For safety analyses, all AEs and SAEs are reported. No SAR was observed.

Safety endpoints were all cause death, cardiac and non-cardiac hospitalizations, worsening heart failure (worsening dyspnea and worsening or new edema), coronary heart disease (myocardial infarction, revascularization or new symptoms of angina pectoris), significant renal impairment (decrease of eGFR below 30mL/min/1.73m², or a decrease of eGFR >15mL/min/1.73m², compared to baseline) and Anemia (de novo, according to WHO criteria; or a decrease of hemoglobin levels >1g/dl in anemic patients), increases in serum potassium above 5.0mmol/L, occurrence of gynecomastia, and self-reported intolerance of the study medication. Comparisons were carried out by the t-test for quantities and Fisher's exact test for binary variables.

16.4 Subgroup analyses

Pre-specified subgroup analyses were performed by ANCOVA with the follow-up value of the endpoint as the dependent variable, respective baseline variable as covariate and treatment, subgroup variable and their interaction term as factor variables. Patients were categorized into subgroups by each of the following variables at baseline (median split was used for continuous variables): age, sex, body mass index, systolic blood pressure, heart rate, NYHA class (II or III), grade of diastolic function (I° versus all other), criteria for diastolic heart failure according to ESC criteria (Paulus positive or negative),[22] and eGFR.

17 Summary

17.1 Patients

Of 795 patients screened from March 2007 to April 2011, 422 were included and randomized to receive spironolactone (n=213) or placebo (n=209); 400 were included in the primary analysis (see consort flow diagram).

The mean length of follow-up was 11.6±1.8months, and the mean daily dose of spironolactone was 21.6±8.1mg. Individual reasons for not attending the follow-up visits are shown in detail in Consort flow diagram. Of 400 patients attending the 12-month follow-up visit, two (one in each arm) refused to undergo the examinations for both primary endpoints, and n=24 (n=8 placebo, n=16 spironolactone) were unable to undergo CPET for orthopaedic reasons (current pain or preceding surgery in the hip, knee or lower legs).

Baseline characteristics were similar between treatment groups (Table 17.1).

Table 17.1. Baseline Characteristics.*

Variable	Total (n=422)	Placebo (n=209)	Spironolactone (n=213)
Demographics			
Age, mean ±SD [yr]	67±8	67±8	67±8
Female sex – no. (%)	221 (52)	110 (53)	111 (52)
Medical History - no. (%)			
Hospitalization for heart failure in past 12 months	156 (37)	75 (36)	81 (38)
Coronary heart disease	170 (40)	78 (37)	92 (43)
Hypertension	387 (92)	190 (91)	197 (92)
Hyperlipidemia	273 (65)	143 (68)	130 (61)
Diabetes mellitus	70 (17)	34 (16)	36 (17)
Chronic obstructive pulmonary disease	14 (3)	3 (1)	11 (5)
Atrial fibrillation	22 (5)	9 (4)	13 (6)
Physical examination - mean ±SD			
BMI - kg/m^2	28.9±3.6	28.9±3.6	28.9±3.6
BP systolic - mmHg	135±18	135±18	135±18
BP diastolic - mmHg	79±11	80±12	79±10

Variable	Total (n=422)	Placebo (n=209)	Spironolactone (n=213)
Heart rate on ECG - bpm	65±13	64±12	66±14
Signs / symptoms - no. (%)			
NYHA functional class			
II	363 (86)	183 (88)	180 (85)
III	59 (14)	26 (12)	33 (15)
Peripheral edema	165 (39)	84 (40)	81 (38)
Nocturia	338 (80)	168 (80)	170 (80)
Paroxysmal nocturnal dyspnea	67 (16)	31 (15)	36 (17)
Nocturnal cough	61 (15)	31 (15)	30 (14)
Fatigue	249 (59)	118 (56)	131 (62)
Current medication – no. (%)			
Angiotensin converting enzyme inhibitor and/or angiotensin receptor antagonist	325 (77)	158 (76)	167 (78)
Beta blocker	302 (72)	156 (75)	146 (69)
Diuretic	227 (54)	109 (52)	118 (55)
Calcium antagonist	105 (25)	58 (28)	47 (22)
Anti-platelet agent	221 (52)	108 (52)	113 (53)
Lipid lowering drug	230 (55)	118 (56)	112 (53)
Anticoagulant	58 (14)	32 (15)	26 (12)
Allopurinol	40 (10)	21 (10)	19 (9)
Antidepressant	30 (7)	13 (6)	17 (8)
Laboratory - mean ±SD			
Sodium - mmol/L	140.3±3.0	140.3±2.7	140.3±3.3
Potassium - mmol/L	4.2±0.4	4.2±0.4	4.2±0.4
Hemoglobin - g/dL	13.8±1.2	13.8±1.3	13.8±1.2
eGFR - mL/min/1.73m^2	79±19	78±18	79±19
NT-proBNP - ng/L – median (inter-quartile range)	158 (83-299)	148 (80-276)	179 (81-276)

17.2 Primary Endpoints

Spironolactone significantly improved diastolic function compared to placebo (Table17.2). E/e' significantly declined with spironolactone from 12.7±3.6 to 12.1±3.7 and increased in the placebo group from 12.8±4.4 to 13.6±4.3 (P<0.001 for difference between groups). The estimated difference from ANCOVA, adjusted for baseline, was –1.5 (95% CI –2.0 to –0.9, P<0.001). This effect was evident at 6 months and was maintained through 12 months.

Peak VO_2 increased from 16.3±3.6 to 16.8±4.6mL/min/kg in the spironolactone group and from 16.4±3.5 to 16.9±4.4mL/min/kg in the placebo group, without a difference between groups (P=0.67). The estimated difference from ANCOVA, adjusted for baseline, was -0.1mL/min/kg (95% CI –0.6 to +0.8, P=0.81) for spironolactone versus placebo.

Table 17.2. Primary Endpoints after 12 Months.

Variable	Placebo	Spironolactone	Difference Spironolactone–Placebo	
			Difference (95% CI)	P-value
Primary echocardiographic endpoint	**(n=195)**	**(n=203)**		
E/e' (medial) velocity ratio	13.6±4.3	12.1±3.7	–1.5 (–2.0 to –0.9)	<0.001
Primary spiroergometric	**(n=187)**	**(n=187)**		

endpoint				
Peak VO_2 - mL/min/kg	16.9±4.4	16.8±4.6	– 0.1 (–0.6 to +0.8)	0.81

The beneficial effect on E/e' was consistent across all pre-specified subgroups (Figure 17.1).

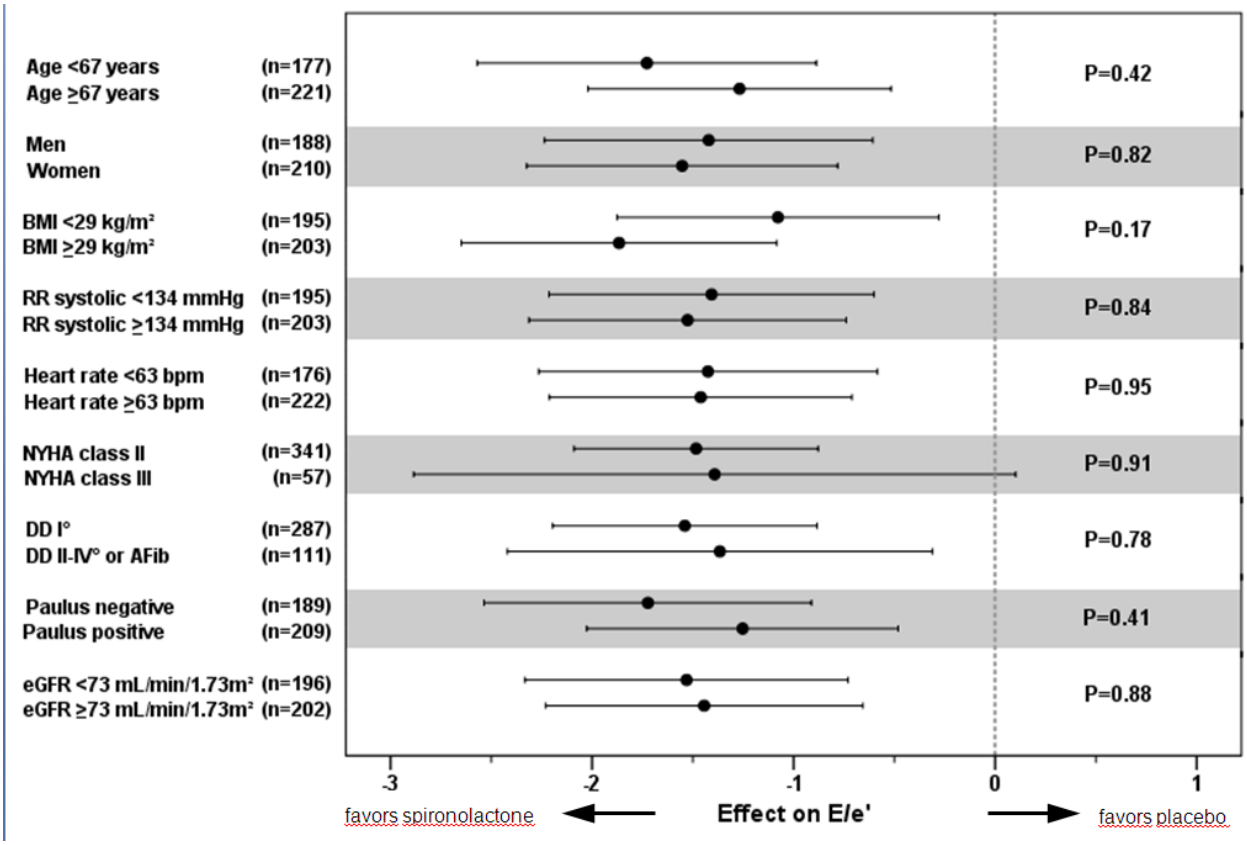


Figure 17.1: Ratio of E/é in pre-defined subgroups according to the assigned treatment

As shown in Figure 17.2 the absence of an effect on peak VO_2 was consistent across all pre-specified subgroups.

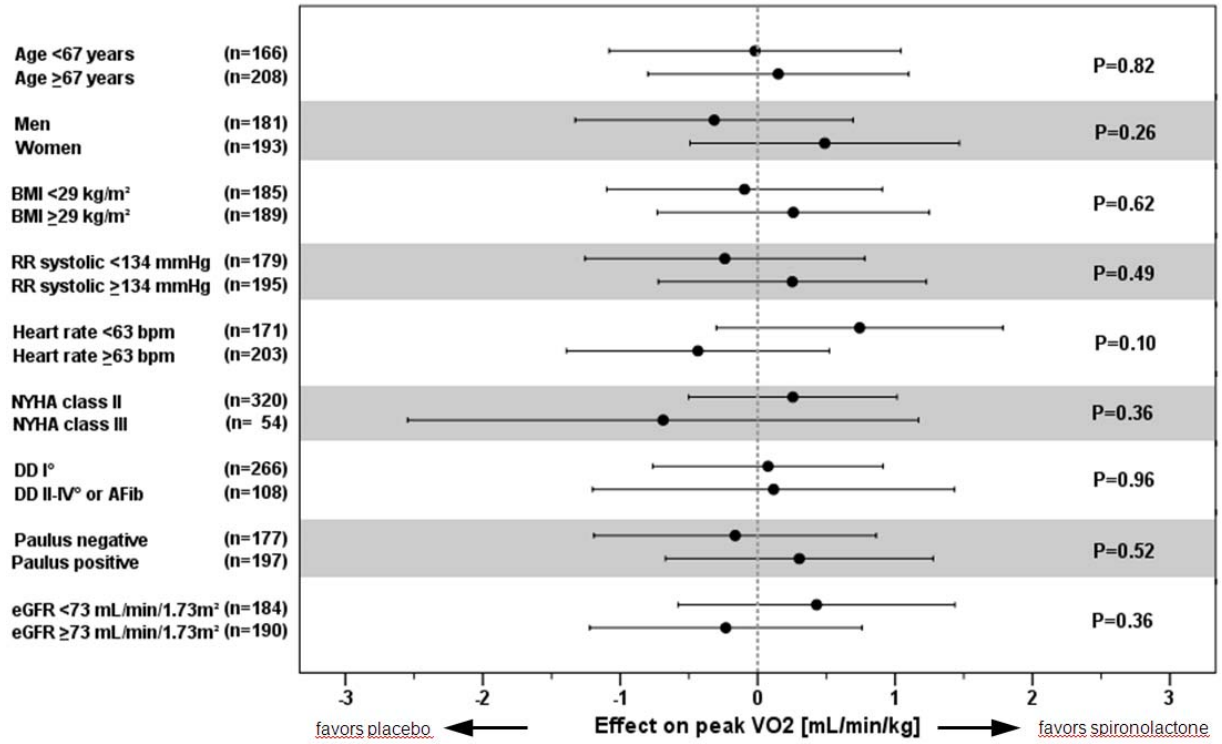


Figure 17.2: Ratio of peak VO_2 in pre-defined subgroups to the assigned treatment

17.3 Secondary Endpoints

Secondary echocardiographic outcome measures of cardiac function and remodeling

Spironolactone improved major parameters of cardiac function and remodeling (Table 17.3). The improvement in the E/e' ratio at 12 months was attributable to both lower E (P=0.03) and higher e' (P=0.002).

Left ventricular ejection fraction increased (P=0.04), while left ventricular end-diastolic diameter (P=0.01), and left ventricular mass index (P=0.009) decreased significantly in the spironolactone group compared to placebo. Other measures of diastolic function or cardiac structure did not differ significantly between spironolactone and placebo.

Table 17.3: Echocardiography Results after 12 Months.*

Variable	Placebo (n=195)	Spironolactone (n=203)	Spironolactone–Placebo Difference (95% CI)	P-value
Secondary endpoints				
E wave velocity - cm/s	73.6±21.5	70.5±16.3	–2.5 (–4.9 to –0.2)	0.03
Medial e' wave velocity - cm/s	5.86±1.48	6.16±1.54	+0.36 (+0.13 to +0.60)	0.002
E/A velocity ratio	0.96±0.34	0.91±0.31	–0.04 (–0.09 to +0.01)	0.08
Isovolumic relaxation time - ms	88±26	86±27	–3 (–8 to +2)	0.28
Deceleration time - ms	238±65	241±63	+6 (–6 to +18)	0.32
Grade of diastolic dysfunction – no. (%)			0.63 (OR: 0.37 to 1.09)	0.10
no diastolic dysfunction	2 (1)	4 (2)		
I	129 (68)	143 (75)		

Variable	Placebo (n=195)	Spironolactone (n=203)	Spironolactone–Placebo Difference (95% CI)	P-value
II	57 (30)	43 (23)		
III	0 (0)	1 (<1)		
IV	2 (1)	0 (0)		
n.d. for atrial fibrillation	5	12		
LV ejection fraction - %	66±8	67±8	+2 (0 to +3)	0.04
LV mass index – g/m^2	106±28	100±27	–6 (–10 to –1)	0.009
Left atrial volume index - mL/m^2	27.6±7.3	27.5±9.3	–0.4 (–1.5 to +0.8)	0.51
LV diameter (end diastolic) - mm	46.4±6.5	44.6±6.4	–1.4 (–2.5 to –0.3)	0.01
LV diameter (end systolic) - mm	26.5±6.4	25.5±6.2	–0.6 (–1.8 to +0.5)	0.26

* Plus - minus values are means ± SD, LV, left ventricular; E, peak early transmitral ventricular filling velocity; e', early diastolic tissue Doppler velocity

Secondary outcome measures of exercise performance

After 12 months, maximal exercise capacity (peak VO_2), duration of exercise, ventilatory anaerobic threshold (workload and oxygen consumption) and Borg scale were not different between the two groups, but VE/VCO_2 slope slightly increased (P=0.04, Table 17.4).

Table 17.4: Cardiopulmonary Exercise Testing Results after 12 Months.*

Variable	Placebo (n=187)	Spironolactone (n=187)	Difference Spironolactone–Placebo Difference (95% CI)	P-value
Secondary endpoints				
AT VO_2 - mL/min/kg	12.1±3.4	11.9±3.7	–0.3 (–1.0 to +0.4)	0.39
V_E/VCO_2 slope	31.5±5.0	31.8±4.6	+0.8 (0 to +1.5)	0.04
Borg scale	4.6±1.9	4.6±2.1	+0.1 (–0.3 to +0.5)	0.40
Anaerobic threshold – W	66±24	65±26	–1 (–5 to +4)	0.79
Duration of exercise - s	547±188	540±193	+10 (–8 to +28)	0.27
Maximal workload – W	101±32	100±33	+2 (–2 to +5)	0.35

* Plus - minus values are means ±; VE/VCO_2, minute ventilation to carbon dioxide output ratio; AT VO_2, oxygen consumption at anaerobic threshold;

Secondary clinical outcome parameters

6-minute walking distance slightly decreased in the spironolactone group after 12 months (P=0.02, Table 17.5).

The improved cardiac function and structure with spironolactone was accompanied by a significant decrease in NT-proBNP levels (P=0.03). Spironolactone significantly reduced systolic blood pressure after 12 months compared to placebo (P<0.001, Table 17.5). Heart failure symptoms assessed by NYHA class were not significantly altered by spironolactone treatment.

Table 17.5: Clinical and Laboratory Results, and Quality of Life after 12 Months.*

Variable	Placebo (n=196)	Spironolactone (n=204)	Difference Spironolactone–Placebo Difference (95% CI)	P-value
Six-minute walk test				
Six-minute walk distance - m –	536±102	517±94	–15 (–27 to –2)	0.02
Laboratory secondary endpoint				
NT-proBNP - ng/L – median (inter-quartile range)	165 (82-314)	152 (77-307)	0.86 (0.75 to 0.99) (geometric mean ratio)	0.03
Other clinical variables				
NYHA class – no. (%)				
I	11 (6)	8 (4)	1.30 (0.70 to 2.40) (odds ratio)	0.41
II	172 (88)	178 (87)		
III	13 (7)	18 (9)		
Peripheral edema – no. (%)	71 (36)	61 (30)	0.69 (0.42 to 1.14) (odds ratio)	0.15
BP systolic - mmHg	137±16	128±16	–8 (–11 to –5)	<0.001
BP diastolic - mmHg	80±11	77±10	–3 (–5 to –2)	<0.001
Mean arterial pressure [mmHg] – mean±SD	99±11	94±11	–5 (–7 to –3)	<0.001
Puls pressure [mmHg] – mean±SD	56±14	52±14	–5 (–7 to –2)	<0.001
Heart rate on ECG - bpm	65±11	66±12	+1 (–1 to +3)	0.56
Other laboratory variables				
Sodium - mmol/L	140.4±2.8	139.5±3.1	–0.9 (–1.4 to –0.5)	<0.001
Potassium - mmol/L	4.1±0.4	4.4±0.4	+0.2 (+0.1 to +0.3)	<0.001
eGFR - mL/min/1.73m^2	74±19	69±18	–5 (–8 to –3)	<0.001

Quality of life secondary endpoints

Similarly, effects on quality of life and depressive symptoms did not differ between both groups (Table 17.6).

Table 17.6: Quality of Life after 12 Months.*

Variable	Placebo (n=187)	Spironolactone (n=194)	Difference Spironolactone–Placebo Difference (95% CI)	P-value
Minnesota Living With Heart Failure Questionnaire, total score	21±17	21±17	0.0 (–2 to +2)	0.97
SF-36 Physical Functioning scale	66±22	64±24	+1 (–2 to +4)	0.62
SF-36 Global self assessment	3.3±0.6	3.3±0.7	+0.0 (-0.1 to +0.1)	0.79
Symptoms of depression (PHQ-9 sum score)	5.6±4.1	5.5±4.2	–0.1 (–0.7 to +0.5)	0.72
HADS-Anxiety	5.0±3.7	4.7±3.7	-0·.4 (-0.9 to +0.1)	0.14
HADS-Depression	4.7±3.7	4.4±3.6	-0.5 (-1.0 to +0.0)	0.07

* Plus - minus values are means ± SD, SF-36, 36 Item Short Form Health Survey; PHQ, 9 Item depression scale of the Patient Health Questionnaire; HADS, Hospital Anxiety and Depression Scale

17.4 Safety results

The main Safety and adherence data are shown in Table 17.7. Adherence was similar in both groups (92±20% vs. 93±19%, P=0.44).

The number of cardiovascular events was relatively low. A mild increase in potassium levels and a decrease in eGFR occurred in the spironolactone group. These changes were evident after 1 week of therapy and remained stable thereafter. A significantly greater proportion of patients randomized to spironolactone experienced potassium serum levels greater than 5.0 mmol/L, but there was no difference between groups in the incidence of serious hyperkalemia (>5.5 mmol/L) and no patients were hospitalized for hyperkalemia.

Of all adverse events, only gynecomastia (P=0.003 for intolerance; P=0.03 for dose reduction) and an increase of potassium serum levels to greater than 5.0 mmol/L (P<0.001) during follow-up were significantly associated with subjective intolerance or reduction or stopping of the study medication.

Table 17.7: Adverse Events and Adherence.

Variable - no. (%)	Placebo	Spironolactone	P-value
Adverse events			
Death	0 (0)	1 (<1)	1.00
Hospitalization	50 (24)	60 (28)	0.38
Cardiac hospitalization	15 (7)	21 (10)	0.38
Non-cardiac hospitalization	37 (18)	47 (22)	0.27
Worsening dyspnea	32 (15)	33 (15)	1.00
New or worsening edema	44 (21)	35 (16)	0.26
Worsening coronary heart disease	29 (14)	33 (15)	0.68
Myocardial infarction	3 (1)	5 (2)	0.72
Worsening renal function	43 (21)	77 (36)	<0.001
eGFR <30 mL/min/1.73m^2 at last visit	1 (<1)	3 (1)	0.62
New or worsening Anemia	18 (9)	34 (16)	0.03
Anemia at last visit	20 (10)	33 (15)	0.08
Serum potassium			
ever increased >5.0 mmol/L	22 (11)	44 (21)	0.005
>5.0 mmol/L at last visit	7 (3)	13 (6)	0.25
ever increased >5.5 mmol/L	3 (1)	4 (2)	1.00
>5.5 mmol/L at last visit	1 (<1)	1 (<1)	1.00
Gynecomastia	1 (<1)	9 (4)	0.02
Adherence to study medication			
Overall adherence rate - %	93±19	92±20	0.44
Ever reported intolerance	13 (6)	36 (17)	<0.001
Ever reduced dose or stopped	30 (14)	48 (23)	0.03

Plus - minus values are means ± SD, Worsening coronary heart disease defined as myocardial infarction, revascularization or occurrence of angina pectoris at follow-up; worsening renal function defined as worsening as reported by the physician, decrease of eGFR below 30mL/min/1·73m², or a decrease of eGFR >15mL/min/1·73m² compared to baseline; new or worsening Anemia defined as new diagnosed Anemia according to WHO criteria or worsening of hemoglobin levels ≥1g/dL during follow-up.

18 Conclusions

We evaluated the effect of adding spironolactone to recommended standard risk factor control in patients with HF with preserved EF. The E/e' ratio, a continuous parameter of diastolic dysfunction and an estimate of left ventricular end-diastolic filling pressure, was significantly reduced (mean difference compared to placebo, -1.5) in the spironolactone group, whereas the co-primary endpoint peak oxygen consumption at maximal exercise remained unchanged. The beneficial effect of spironolactone on diastolic function and the neutral effect on exercise capacity were consistent across all pre-specified subgroups.

Spironolactone also improved secondary endpoints of cardiac remodeling, including a reduction in left ventricular mass index and NT-proBNP levels, both of which are independent predictors of heart failure hospitalizations and cardiovascular death in HF with preserved EF. Secondary endpoints of heart failure symptoms (assessed by NYHA class or Borg dyspnea scale during CPET), and quality of life measures (Minnesota Living With Heart Failure Questionnaire, SF-36 Physical Functioning Scale, SF-36 Global Self Assessment) did not change. Moreover, sub-maximal exercise capacity (six-minute walk distance) decreased.

Similar reverse remodeling effects of spironolactone have been detected in patients with HF with reduced EF (HfrEF), a condition in which spironolactone treatment also reduces all-cause mortality and heart failure hospitalizations. Interestingly, although MR antagonism therapy is associated with reverse remodeling and improved prognosis in HF with reduced EF, it does not improve peak VO_2 or quality of life in this population. In a recent meta-analysis of 1.575 patients with HF with reduced EF, aldosterone antagonists improved NYHA functional status by only 0.13 classes, an effect size our study was not powered to detect. Whether MRAs may also improve prognosis in HF with preserved EF is currently being investigated in the international NIH-funded TOPCAT trial.

Activation of the MR system by aldosterone promotes hypertension, endothelial dysfunction, left ventricular hypertrophy and myocardial fibrosis. ACE inhibitors and angiotensin receptor blockers (ARB) inhibit angiotensin II-mediated aldosterone release, but despite optimized therapy, a large proportion of patients with heart failure have elevated aldosterone plasma levels (aldosterone escape). Spironolactone is a competitive antagonist of aldosterone at the MR, and it has been shown to decrease extracellular matrix turnover and myocardial collagen content, mechanisms which are known to influence the progression of heart failure.

Aldo-DHF is the first large, multi-center trial to demonstrate structural reverse cardiac remodeling in symptomatic HF with preserved EF patients treated with standard medications for risk factor control. ACE inhibitor or ARB therapy was prescribed in 77% of patients, and 72% were on a beta-blocker at randomization. Thus, the reverse remodeling effects of spironolactone were observed on top of substantial anti-neuroendocrine background therapy. Importantly, earlier pharmacological interventions in HF with preserved EF have failed to improve diastolic dysfunction, the major underlying cardiac pathophysiology in HF with preserved EF. ARBs and beta blockers have not induced either functional or clinical outcome improvements in randomized trials. Hence, spironolactone is the first drug to show an improvement in diastolic function among HF with preserved EF patients in a randomized, double-blind, and placebo-controlled clinical trial.

Compared to placebo, spironolactone resulted in a substantial blood pressure reduction (-8mmHg; 95% CI -11 to -5 systolic, and -3mmHg; -5 to -2 diastolic, both p<0.001), which could explain improved diastolic function and reverse remodeling. However, after adjustment for baseline and follow-up blood pressure values the effects of spironolactone on diastolic function (E/e': -1.1; 95% CI -1.6 to -0.5, P<0.001) and left ventricular mass index (LVMI: -4.8g/m²; -9.4 to -0.3, P=0.04) remained statistically significant, suggesting that the reverse remodeling effects of spironolactone are independent of blood pressure reduction. In contrast, enalapril or nebivolol decreased blood pressure without effects on diastolic function or structural remodeling in HF with preserved EF. Although the mean blood pressure reduction by spironolactone in Aldo-DHF was 5mmHg lower than that observed in the VALIDD study

with valsartan, spironolactone treatment lowered E/e', neuroendocrine activation, and left ventricular mass index, whereas valsartan had no overall effect on these parameters.

Unexpectedly, the beneficial effects of spironolactone on diastolic function were not associated with any clinical improvement. Our study population may have been too young or too healthy, or the treatment period may have been too short to see a translation of improved diastolic function into a clinical benefit. The observed placebo event rate in Aldo-DHF was lower than that in clinical trials of MRAs in HF with reduced EF, indicating a lower severity of illness or less progressive heart failure. Thus, in the Aldo-DHF population that likely represented early stage HF with preserved EF, longer follow-up may have been needed to fully evaluate the potential effects of spironolactone on symptomatic or clinical outcome endpoints. TOPCAT will clarify the impact of MR antagonism on clinical outcomes. Also, the observed 2.8 percent reduction in submaximal exercise capacity (six-minute walking distance) in the spironolactone group warrants consideration. Though this decline appears clinically irrelevant, it could be explained by the modest decrease in renal function, the yet unexplained decrease in hemoglobin levels, or external factors such as assessment technique, patient motivation, or statistical chance. Nevertheless, the lack of meaningful beneficial effects of spironolactone on various measures of exercise capacity and quality of life suggests that besides LV structural and functional remodeling, other mechanisms also contribute to impaired functional capacity in HF with preserved EF.

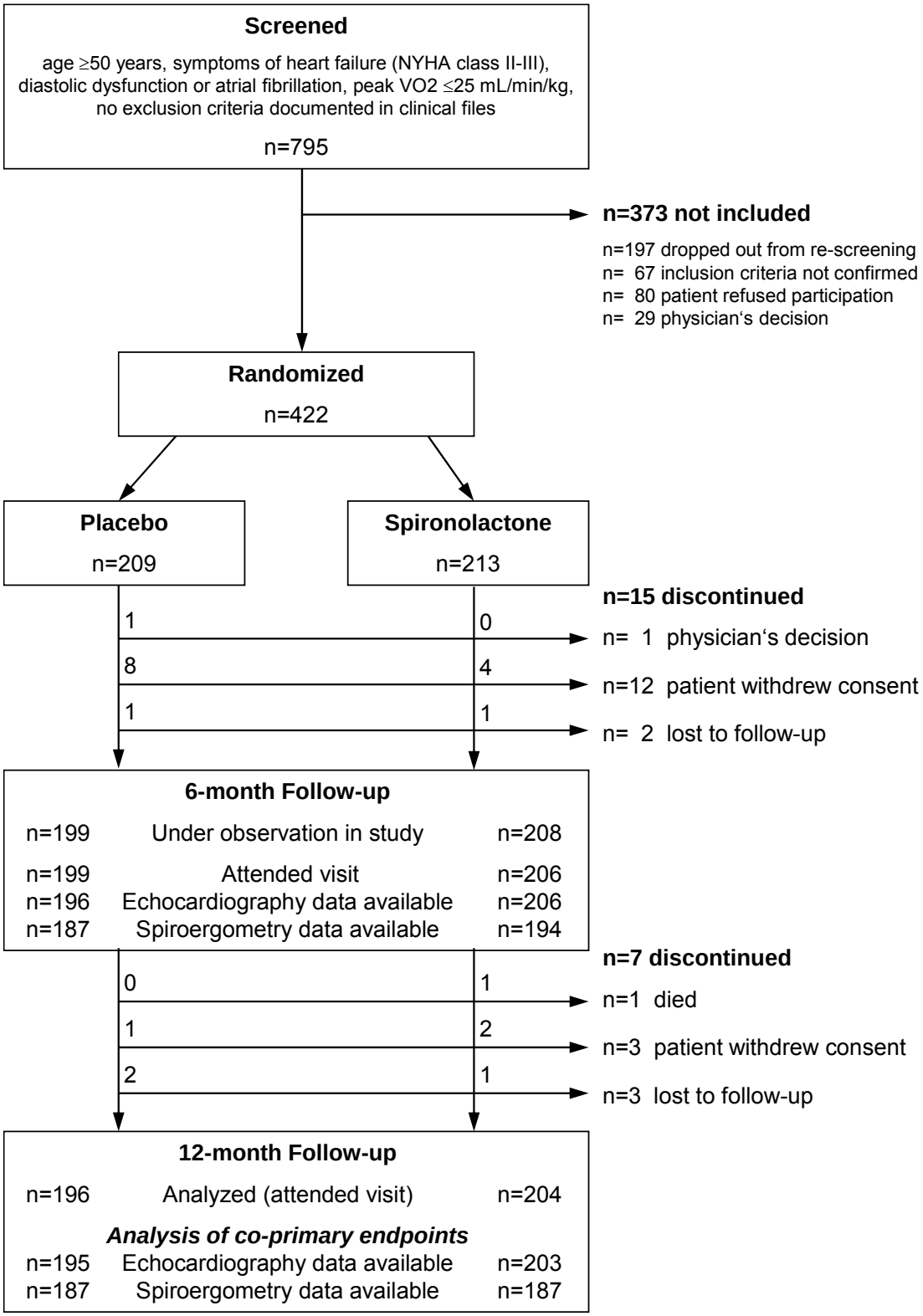
As anticipated and observed in previous studies, spironolactone increased potassium levels by an average of 0.2mmol/L. Of note, clinically relevant hyperkalemia (potassium >5.5mmol/L) was rare (1.9% in the spironolactone group, 1.4% in the placebo group, p=1.00), potassium levels never exceeded 5.8 mmol/L, and no hospitalizations for hyperkalemia occured. Observational data after the publication of the RALES study in HF with reduced EF have shown that inadequately high doses of spironolactone and less rigorous control of risk factors for hyperkalemia in daily practice may shift the benefit/risk ratio of spironolactone towards harm. Thus, adherence to recommended exclusion criteria, dosing guidelines, and regular monitoring of potassium levels and renal function is recommended.

The present results should be interpreted in the context of several limitations. The Aldo-DHF study population consisted of stable patients with moderate heart failure symptoms. The results may not apply to patients with more severe disease and more comorbidities. However, at later stages, HF with preserved EF patients more often die from non-cardiovascular causes. Therefore, an intervention with an impact on cardiac structure and function at an earlier phase of the disease as tested in Aldo-DHF seems attractive. On the other hand, the relatively stable Aldo-DHF patient population, in association with only moderately reduced sub-maximal and maximal exercise performance measures, may have precluded translation of cardiac functional and structural improvements into better exercise tolerance and quality of life. Importantly, Aldo-DHF was not powered to evaluate the effect of spironolactone on heart failure hospitalizations or mortality.

In conclusion, Aldo-DHF showed that, compared with placebo, spironolactone treatment in HF with preserved EF patients improved diastolic function and left ventricular remodeling, but it did not alter maximal exercise capacity in the population studied. These data provide further support to the hypothesis that MR antagonists may induce regression of the underlying pathophysiology of diastolic dysfunction present in the majority of patients with HF with preserved EF. Additional prospective, randomized, and adaequately powered studies are warranted to further evaluate the effect of improving diastolic function on symptomatic, functional, and clinical outcome endpoints.

19 Appendices

19.1 CONSORT Flow Diagramm



19.2 Information about the amendments in the study conduct

The version of the trial protocol final 1.1 (2007-01-10 was approved by the regulatory authority and positively evaluated by the lead ethics committee.

The contents of the Amendment 01 (final 1.1; 2008-04-17) were:

- Inclusion of patients with atrial fibrillation
- Change of cut off of peak VO2 (from peak VO2 ≤ 20 ml/kg/min to peak VO2 ≤ 25 ml/kg/min)
- Removal of existing trial sites

The contents of the Amendment 01 (final 1.0; 2009-10-26) were:

- Prolongation of Trial Duration from three to five years
- Documentation and reporting of adverse events (AE/SAE; only occurred after randomisation)
- Announcement of new trial sites / removal of existing trial site
- Notification of new investigators

The contents of the Amendment 03 (final 1.1; 2010-11-29) were:

- Announcement of a new trial site / removal of an existing trial site
- Notification of new investigators

19.3 Abbreviations

6MWT	six-minute walk testing
A	peak atrial transmitral inflow
ACE	angiotensin converting enzyme
AE	Adverse Event
AR	pulmonary venous peak atrial contraction reversed velocity (echocardiography)
ARB	angiotensin receptor blockers
AT VO_2	oxygen consumption at anaerobic threshold
BMI	body mass index
BP	blood pressure
CABG	coronary artery bypass graft
CI	confidence interval
CPET	cardiopulmonary exercise testing
DT	deceleration time (echocardiography)
dur	duration
E	peak early transmitral ventricular filling velocity (echocardiography)
E'	early diastolic tissue Doppler velocity (echocardiography)
EF	ejection fraction
eGFR	estimated glomerular filtration rate
FEV1	forced expiratory volume in one second
FPI	Firste Patient In
HADS	Hospital Anxiety and Depression Scale
HF	Heart Failure
HFpEF	heart failure with preserved ejection fraction
IVRT	Isovolumic relaxation time
LA	left atrium
LPO	Last Patient Out
LVMI	left ventricular mass index

LVEF	left ventricular ejection fraction
MLWHFQ	Minnesota Living With Heart Failure Questionnaire
MR	Mineralocorticoid receptor
MRA	Mineralocorticoid receptor antagonists
NT-proBNP	N-terminal cleavage product of pro B-type natriuretic peptide
NYHA	New York Heart Association
QoL	quality of life
peak VO_2	peak oxygen uptake
PHQ	9 Item depression scale of the Patient Health Questionnaire
RR	blood pressure
SAE	serious adverse event
SD	standard deviation
S/D	systolic-to-diastolic pulmonary venous flow ratio (echocardiography)
SF-36	36 Item Short Form Health Survey
Tei-Index	myocardial performance index
VC	vital capacity
VE/VCO_2	minute ventilation to carbon dioxide output ratio
V_p	color M-mode flow propagation velocity (echocardiography)