Effect of Spironolactone on Diastolic Function and Exercise Capacity in Patients With Heart Failure With Preserved Ejection Fraction

The Aldo-DHF Randomized Controlled Trial

Frank Edelmann, MD
Rolf Wachter, MD
Albrecht G. Schmidt, MD
Elisabeth Kraigher-Krainer, MD
Caterina Colantonio, MD
Wolfram Kamke, MD
André Duvinage, MD
Raoul Stahrenberg, MD
Kathleen Durstewitz, MD
Markus Löffler, MD
Hans-Dirk Düngen, MD
Carsten Tschöpe, MD
Christoph Herrmann-Lingen, MD
Martin Halle, MD
Gerd Hasenfuss, MD
Götz Gelbrich, PhD
Burkert Pieske, MD
for the Aldo-DHF Investigators

Importance Diastolic heart failure (ie, heart failure with preserved ejection fraction) is a common condition without established therapy, and aldosterone stimulation may contribute to its progression.

Objective To assess the efficacy and safety of long-term aldosterone receptor blockade in heart failure with preserved ejection fraction. The primary objective was to determine whether spironolactone is superior to placebo in improving diastolic function and maximal exercise capacity in patients with heart failure with preserved ejection fraction.

Design and Setting The Aldo-DHF trial, a multicenter, prospective, randomized, double-blind, placebo-controlled trial conducted between March 2007 and April 2012 at 10 sites in Germany and Austria that included 422 ambulatory patients (mean age, 67 [SD, 8] years; 52% female) with chronic New York Heart Association class II or III heart failure, preserved left ventricular ejection fraction of 50% or greater, and evidence of diastolic dysfunction.

Intervention Patients were randomly assigned to receive 25 mg of spironolactone once daily (n=213) or matching placebo (n=209) with 12 months of follow-up.

Main Outcome Measures The equally ranked co–primary end points were changes in diastolic function (E/e') on echocardiography and maximal exercise capacity (peak $\dot{V}O_2$) on cardiopulmonary exercise testing, both measured at 12 months.

Results Diastolic function (E/e') decreased from 12.7 (SD, 3.6) to 12.1 (SD, 3.7) with spironolactone and increased from 12.8 (SD, 4.4) to 13.6 (SD, 4.3) with placebo (adjusted mean difference, −1.5; 95% CI, −2.0 to −0.9; $P<.001$). Peak $\dot{V}O_2$ did not significantly change with spironolactone vs placebo (from 16.3 [SD, 3.6] mL/min/kg to 16.8 [SD, 4.6] mL/min/kg and from 16.4 [SD, 3.5] mL/min/kg to 16.9 [SD, 4.4] mL/min/kg, respectively; adjusted mean difference, +0.1 mL/min/kg; 95% CI, −0.6 to +0.8 mL/min/kg; $P=.81$). Spironolactone induced reverse remodeling (left ventricular mass index declined; difference, −6 g/m^2; 95% CI, −10 to −1 g/m^2; $P=.009$) and improved neuroendocrine activation (N-terminal pro–brain-type natriuretic peptide geometric mean ratio, 0.86; 95% CI, 0.75-0.99; $P=.03$) but did not improve heart failure symptoms or quality of life and slightly reduced 6-minute walking distance (–15 m; 95% CI, –27 to –2 m; $P=.03$). Spironolactone also modestly increased serum potassium levels (+0.2 mmol/L; 95% CI, +0.1 to +0.3; $P<.001$) and decreased estimated glomerular filtration rate (−5 mL/min/1.73 m^2; 95% CI, −8 to −3 mL/min/1.73 m^2; $P<.001$) without affecting hospitalizations.

Conclusions and Relevance In this randomized controlled trial, long-term aldosterone receptor blockade improved left ventricular diastolic function but did not affect maximal exercise capacity, patient symptoms, or quality of life in patients with heart failure with preserved ejection fraction. Whether the improved left ventricular function observed in the Aldo-DHF trial is of clinical significance requires further investigation in larger populations.

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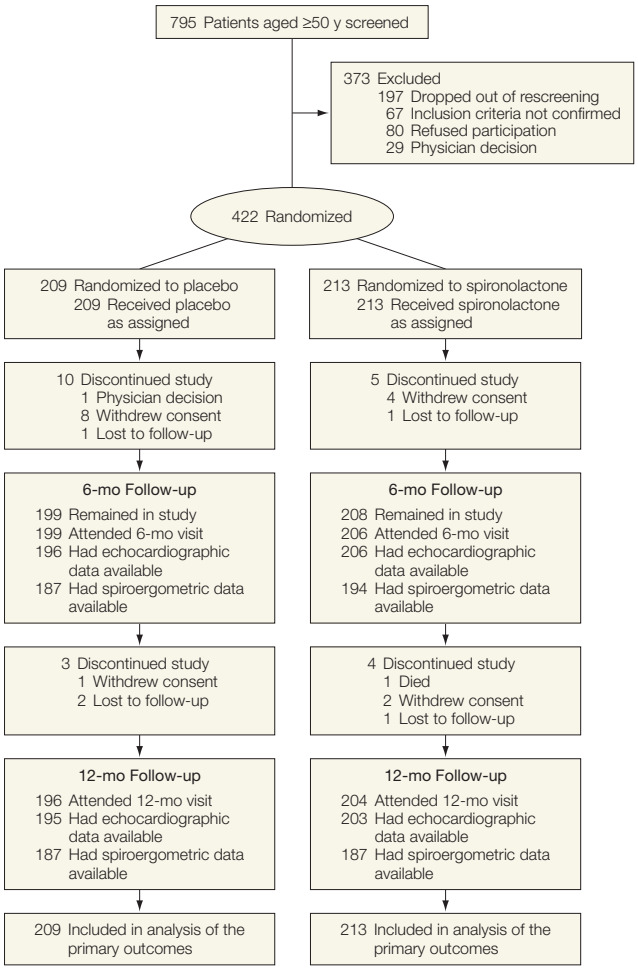
Heart failure (HF) with preserved ejection fraction (EF) accounts for more than 50% of the total HF population.[1] Community-based cohort studies have shown that mortality rates are similar in HF with preserved EF compared with HF with reduced EF,[1] but data from large clinical trials point toward a better outcome in HF with preserved EF. This may indicate that comorbidities that are typically excluded in trials may contribute to the poor prognosis in HF with preserved EF.[1-6] Left ventricular diastolic dysfunction and adverse cardiac remodeling are considered major

For editorial comment see p 825.

Author Affiliations are listed at the end of this article.
A complete list of the Aldo-DHF Investigators appears in the eAppendix.

Corresponding Author: Burkert Pieske, MD, Department of Cardiology, Medical University Graz, Auenbruggerplatz 15, A-8010 Graz, Austria (burkert.pieske@medunigraz.at).

Figure 1. Participant Flow



underlying pathologies in HF with preserved EF.[7] However, pharmacotherapies tested to date have not shown improvements in diastolic dysfunction, cardiac remodeling, or cardiovascular outcome.[3-6]

Mineralocorticoid receptor activation by aldosterone contributes to the pathophysiology of HF (regardless of EF) through several mechanisms, including sodium retention, potassium loss, endothelial dysfunction, vascular inflammation, fibrosis, and hypertrophy.[8,9] The mineralocorticoid receptor antagonists spironolactone and eplerenone reduce total and cardiovascular mortality across the spectrum of HF with reduced EF and in patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure.[10-12] Although small preliminary studies suggest that mineralocorticoid receptor antagonists might also be effective in hypertensive heart disease and diastolic heart failure, no adequately powered clinical trials have been conducted to investigate the effects of chronic mineralocorticoid receptor blockade on structural and functional end points in HF with preserved EF.[13,14]

The Aldosterone Receptor Blockade in Diastolic Heart Failure (Aldo-DHF) trial was designed to address this knowledge gap by evaluating the effects of spironolactone on diastolic function and exercise capacity in patients with HF with preserved EF.[15]

METHODS

Trial Design and Oversight

The Aldo-DHF trial was a multicenter, randomized, placebo-controlled, double-blind, two-armed, parallel-group study that enrolled patients from 10 trial sites in Germany (GE) and Austria (AT). The study design has been previously published.[15] The protocol and amendments were approved by the institutional review board at each participating center, and the trial was conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and local and national regulations. Written informed consent was provided by all patients before any study-related procedures were performed.

The trial was designed and implemented by the principal investigator, the study coordinator, core laboratory guarantors, and the Coordination Center for Clinical Trials Leipzig (University of Leipzig). The Coordination Center for Clinical Trials Leipzig was responsible for all aspects related to site monitoring, data collection, and data management. An independent data and safety monitoring board reviewed the safety data on an ongoing, predefined basis throughout the trial. Patients, the investigator team, individuals performing the assessments, and data analysts remained blinded to the identity of treatment until after database lock; analyses were performed according to a predefined statistical analysis plan.

Participants

The complete eligibility criteria have been published.[15] Briefly, men and women aged 50 years or older were eligible to participate in the study if they had current heart failure symptoms consistent with New York Heart Association (NYHA) class II or III, left ventricular ejection fraction (LVEF) of 50% or greater, echocardiographic evidence of diastolic dysfunction (grade ≥I) or atrial fibrillation at presentation, and maximum exercise capacity (peak $\dot{V}O_2$) of 25 mL/kg/min or less.

Major exclusion criteria included prior documented reduced left ven-

tricular ejection fraction (LVEF ≤40%), significant coronary artery disease (current angina pectoris or ischemia on stress tests; untreated coronary stenosis >50%), myocardial infarction or coronary artery bypass graft surgery 3 months or less prior to enrollment, clinically relevant pulmonary disease (vital capacity <80% or forced expiratory volume in 1 second <80% of reference values on spirometry), significant laboratory abnormalities (potassium ≥5.1 mmol/L; hemoglobin ≤11 g/dL; hematocrit ≤33%; serum creatinine >1.8 mg/dL; or estimated glomerular filtration rate [eGFR]<30 mL/min/1.73 m^2, calculated using the Modification of Diet in Renal Disease formula: 186 × [serum creatinine {in micromoles per liter}/88.4] − 1.154 × age [in years] − 0.203 × 1.21 [if patient is black] × 0.742 [if patient is female]), known contraindications for spironolactone or known intolerance to or therapy with a mineralocorticoid receptor antagonist within the last 3 months, concomitant therapy with a potassium-sparing diuretic (eg, triamterene, amiloride), or potassium supplementation.

Study Drug Administration and Study Procedures

Eligible patients were randomly assigned to receive either spironolactone (25 mg/d) or matching placebo. The randomization ratio was 1:1 for spironolactone or placebo using the Pocock minimization algorithm.[16] Randomization was stratified by grade of diastolic dysfunction (I vs II-III), rhythm (sinus vs other), and study center. The allocation sequence was implemented remotely via Internet/fax by the Coordination Center for Clinical Trials Leipzig. Standard therapies for risk factor and symptom control were at the discretion of treating physicians and required to be unchanged within the 2 weeks prior to randomization.

Production of identical matching placebo and quality control, packaging, labeling, storage, and dispensing of both spironolactone and placebo were performed by Allphamed PHARBIL. The first dose of study drug was administered immediately after randomization under the supervision of the local investigator. No further up-titration was planned.

The study drug could be decreased temporarily to 25 mg every other day for a potassium level greater than 5.2 mmol/L or in the presence of other reversible, non–life-threatening adverse effects. For safety reasons, study medication was stopped for relevant hyperkalemia (serum potassium >5.5 mmol/L) and/or hyperkalemia-associated clinical symptoms, significant renal impairment (serum creatinine >2.5 mg/dL; eGFR <20 mL/min/1.73 m^2), significant breast pain or gynecomastia, or withdrawal of informed consent; rechallenge was encouraged wherever possible. Adherence was assessed at all regularly scheduled visits.

Patients were followed up while receiving blinded study medication for 12

Table 1. Demographic and Clinical Baseline Characteristics[a]

Characteristics	Total (n = 422)	Placebo Group (n = 209)	Spironolactone Group (n = 213)
Demographics			
Age, mean (SD), y	67 (8)	67 (8)	67 (8)
Female	221 (52)	110 (53)	111 (52)
Medical history			
Hospitalization for heart failure in past 12 mo	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)			
Body mass index[b]	28.9 (3.6)	28.9 (3.6)	28.9 (3.6)
Systolic blood pressure, mm Hg	135 (18)	135 (18)	135 (18)
Diastolic blood pressure, mm Hg	79 (11)	80 (12)	79 (10)
Heart rate, /min	65 (13)	64 (12)	66 (14)
Signs and symptoms			
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)
Laboratory measures			
Sodium, mmol/L	140.3 (3.0)	140.3 (2.7)	140.3 (3.3)
Potassium, mean (SD), mmol/L	4.2 (0.4)	4.2 (0.4)	4.2 (0.4)
Hemoglobin, mean (SD), g/dL	13.8 (1.2)	13.8 (1.3)	13.8 (1.2)
eGFR, mean (SD), mL/min/1.73 m^2	79 (19)	78 (18)	79 (19)
NT-proBNP, median (IQR), ng/L	158 (83-299)	148 (80-276)	179 (81-276)
Current medications			
ACE inhibitors/angiotensin receptor antagonists	325 (77)	158 (76)	167 (78)
β-Blockers	302 (72)	156 (75)	146 (69)
Diuretics	227 (54)	109 (52)	118 (55)
Calcium antagonists	105 (25)	58 (28)	47 (22)
Lipid-lowering drugs	230 (55)	118 (56)	112 (53)

Abbreviations: ACE, angiotensin-converting enzyme; eGFR, estimated glomerular filtration rate calculated by Modification of Diet in Renal Disease formula: 186 × (serum creatinine [in micromoles per liter]/88.4)−1.154 × age (in years)−0.203 × 1.21 (if patient is black) × 0.742 (if patient is female); IQR, interquartile range; NT-proBNP, N-terminal pro–brain-type natriuretic peptide; NYHA, New York Heart Association.

[a] Data are expressed as No. (%) unless otherwise specified.

[b] Body mass index is defined as weight in kilograms divided by height in meter squared.

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

Study Objectives and End Points

The primary objective of the Aldo-DHF trial was to determine whether spironolactone is superior to placebo in improving diastolic function and maximal exercise capacity in patients with HF with preserved EF.

The change in E/e' (ie, the relation of peak early transmitral ventricular filling velocity to early diastolic tissue Doppler velocity as an echocardiographic estimate of filling pressure) at 12 months and the change in maximum exercise capacity (peak $\dot{V}O_2$ on cardiopulmonary exercise testing) at 12 months compared with baseline were coequal primary end points.

Prespecified major and additional secondary end points included changes in echocardiographic measures of cardiac function and remodeling, measures of submaximal and maximal exercise capacity, serum biomarkers, and quality of life. Clinical tolerability was assessed as the safety end point. Morbidity and mortality (all-cause and cardiovascular-specific) were also predefined exploratory end points.

Table 2. Echocardiographic, Exercise Testing, and Quality-of-Life Baseline Characteristics[a]

Characteristics	Total (n = 422)	Placebo Group (n = 209)	Spironolactone Group (n = 213)
Echocardiography			
LV ejection fraction, %	67 (8)	68 (7)	67 (8)
LV diameter (end diastolic), mm	46.5 (6.2)	46.9 (6.0)	46.2 (6.4)
LV diameter (end systolic), mm	25.5 (6.4)	25.8 (6.7)	25.2 (6.2)
LV mass index, g/m^2	109 (28)	109 (27)	108 (29)
Men	117 (31)	118 (29)	116 (33)
Women	101 (23)	102 (22)	100 (23)
Left atrial volume index, mL/m^2	28.0 (8.4)	27.8 (7.7)	28.2 (9.1)
E-wave velocity, cm/s	73 (19)	74 (21)	72 (17)
Medial e' wave velocity, cm/s	5.9 (1.3)	6.0 (1.4)	5.9 (1.3)
E/e' (medial) velocity ratio	12.8 (4.0)	12.8 (4.4)	12.7 (3.6)
E/A velocity ratio	0.91 (0.33)	0.92 (0.34)	0.90 (0.31)
Isovolumic relaxation time, ms	89 (26)	88 (25)	89 (26)
Deceleration time, ms	243 (63)	247 (66)	239 (60)
Grade of diastolic dysfunction, No. (%)[b]			
I	307 (77)	151 (75)	156 (78)
II	86 (21)	44 (22)	42 (21)
III	4 (1)	2 (1)	2 (1)
IV	3 (1)	3 (2)	0
Paulus criteria positive, No. (%)	220 (52)	109 (52)	111 (52)
Cardiopulmonary exercise testing			
Duration of exercise, s	540 (176)	545 (176)	535 (176)
Peak $\dot{V}O_2$, mL/min/kg	16.4 (3.5)	16.4 (3.5)	16.3 (3.6)
AT$\dot{V}O_2$, mL/min/kg	11.6 (3.2)	11.4 (3.0)	11.9 (3.4)
$\dot{V}E/\dot{V}CO_2$ slope	30.3 (5.2)	30.7 (5.8)	30.0 (4.6)
Borg scale	5.4 (3.7)	5.4 (2.1)	5.4 (4.8)
Six-minute walk test			
Walk distance, m	530 (87)	531 (86)	529 (88)
Quality of life			
Responded to questionnaire, No. (%)	388 (92)	194 (93)	194 (91)
Minnesota Living With Heart Failure Questionnaire, total score	22 (16)	21 (15)	22 (16)
SF-36 Physical Functioning Scale score	63 (22)	63 (23)	62 (22)
SF-36 Global Self-Assessment score	3.4 (0.6)	3.4 (0.6)	3.4 (0.6)
Symptoms of depression (PHQ-9 summary score)	5.6 (4.1)	5.7 (4.3)	5.6 (3.9)
HADS anxiety score	5.3 (3.8)	5.32 (3.8)	5.28 (3.7)
HADS depression score	4.7 (3.6)	4.7 (3.6)	4.8 (3.6)

Abbreviations: A, peak atrial transmitral ventricular filling velocity; AT$\dot{V}O_2$, oxygen consumption at anaerobic threshold; e', early diastolic tissue Doppler velocity; E, peak early transmitral ventricular filling velocity; HADS, Hospital Anxiety and Depression Scale; LV, left ventricular; PHQ-9, 9-item depression scale of the Patient Health Questionnaire; SF-36, 36-Item Short Form Health Survey; $\dot{V}CO_2$, volume of expired carbon dioxide; $\dot{V}E$, expired volume per unit time; $\dot{V}O_2$, oxygen consumption.

[a] Data are expressed as mean (SD) unless otherwise specified. Higher values indicate better performance for LV ejection fraction, medial e' wave velocity, duration of exercise, peak $\dot{V}O_2$, AT$\dot{V}O_2$, Borg scale, walk distance, SF-36 Physical Functioning Scale, and SF-36 global self assessment. Lower values indicate better performance for left atrial volume index, E/e' (medial) velocity ratio, grade of diastolic dysfunction, $\dot{V}E/\dot{V}CO_2$ slope, Minnesota Living With Heart Failure Questionnaire total score, symptoms of depression (PHQ-9 summary score), HADS anxiety score, and HADS depression score.

[b] Data not measured because of presence of atrial fibrillation: placebo, n=9 (4%); spironolactone, n=13 (6%).

End Point Assessments

Echocardiography. Detailed echocardiography was performed as described previously.[15] All echocardiographic data were reviewed and confirmed at a blinded core laboratory. A standard operating procedure for obtaining all echocardiographic measurements was released before recruitment began, and all participating investigators were trained and certified by the core laboratory staff. Stability of the co–primary end point E/e' (variation ≤20% between screening and baseline visits) was a required inclusion criterion. Diastolic dysfunction was prospectively identified and graded by a prespecified algorithm defined in the study protocol as previously described,[15] and diagnostic criteria for HF with normal EF were used according to current European Society of Cardiology recommendations.[17] Detailed definitions can be found in the eAppendix (available at http://www.jama.com).

Cardiopulmonary Exercise Testing. Standardized cardiopulmonary exercise testing was performed as described previously.[15] All data including validity criteria and protocol adherence were re-

viewed and confirmed at a blinded core laboratory. An standard operating procedure was released before recruitment began, and all participating investigators were trained and certified by the cardiopulmonary exercise testing core laboratory staff. Peak $\dot{V}O_2$ was prospectively defined as the maximum value of the last three 10-second averages during exercise. The variation in peak $\dot{V}O_2$ was required to be 15% or less between screening and baseline.

Quality of Life. The following validated self-rating scales were used for assessing quality of life: the SF-36,[18] the Minnesota Living With Heart Failure Questionnaire,[19] the Patient Health Questionnaire,[20] and the Hospital Anxiety and Depression Scale.[21] Minimal clinically important differences have not been established previously for most of these instruments, and published reports show large variations in methods and suggested minimal clinically important differences, even for identical subscales of the SF-36.[22,23] Hence, the clinical importance of changes in these instruments is subject to future research.

Laboratory Measurements. Venous blood samples were drawn under standardized conditions after 20 minutes of rest in the supine position. Samples were immediately cooled, centrifuged, and processed for storage at −80°C (−112°F). N-terminal pro–brain-type natriuretic peptide (NT-proBNP) was analyzed with the Elecsys NT-proBNP immunoassay (Roche Diagnostics).

Statistical Analyses

For sample size calculation, a gain in peak $\dot{V}O_2$ of 2 mL/min/kg and a decrease in E/e' of 1.2 by spironolactone treatment were assumed. Within-group standard deviations were expected to be 5 mL/min/kg for $\dot{V}O_2$ and 3 for E/e'. Thus, expected mean differences were 0.4 SDs for both primary end points. Global type I and II error rates were set at .05 and .1, respectively (ie, .025 and .05 for each of the 2 primary tests). Thus, 380 evaluable patients (190 in each treatment group) were needed. Assuming a dropout rate of 10%, recruitment of 420 patients was planned.

Analyses of the primary end points were carried out using 2-sided Mann-Whitney *U* tests. All analyses were based on the intention-to-treat principle. Patients who died were assigned the worst rank in both tests, reflecting the worst case of functional loss. A missing value in one of the end points did not preclude analysis of the other. Sensitivity analyses examining the possible effect of missing data on the primary results were performed using last observation carried forward and multiple imputation. Quantitative effects of the intervention were assessed by analysis of covariance with the follow-up value as the dependent variable, treatment as a factor, and the baseline value as the covariate. SPSS version 20 (SPSS Inc) was used as statistical software.

Prespecified secondary end points were changes in anaerobic threshold, slope of expired volume per unit time to volume of expired carbon dioxide ($\dot{V}E/\dot{V}CO_2$), and Borg dyspnea scale during cardiopulmonary exercise testing, E and e' velocities, grade of diastolic dysfunction, left ventricular mass index and left atrial volume index on echocardiography, 6-minute walk distance, NT-proBNP level, and the patient-reported Minnesota Living With Heart Failure Questionnaire total score, SF-36 Physical Functioning scale score, and symptoms of depression measured by the summary score on the 9-item depression scale of the Patient Health Questionnaire. 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 end point.

Analyses were carried out by analysis of covariance, 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. N-terminal 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.

Safety end points were all-cause death, cardiac and noncardiac 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 to <30 mL/min/1.73 m^2 or decrease of eGFR >15 mL/min/1.73 m^2 vs baseline) and anemia (de novo, according to World Health Organization criteria, or decrease of hemoglobin levels >1 g/dL in anemic patients), increases in serum potassium to higher than 5 mmol/L, occurrence of gynecomastia, and self-reported intolerance of the study medication. Comparisons were carried out using the *t* test for quantities and the Fisher exact test for binary variables.

Prespecified subgroup analyses were performed by analysis of covariance with the follow-up value of the end point 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 for continuous variables): age, sex, body mass index, systolic blood pressure, heart rate, NYHA class (II or III), grade of diastolic function (I vs all other), criteria for diastolic heart failure according to European Society of Cardiology criteria (Paulus positive or negative),[17] and eGFR.

RESULTS

Patients

Of 795 patients screened from March 2007 to April 2011, 422 were included and randomized to receive spironolactone or placebo (FIGURE 1). The mean length of follow-up was 11.6 months (95% CI, 11.4-11.8 months) and the mean daily dose of spironolactone was 21.6 mg (95% CI, 20.8-22.3

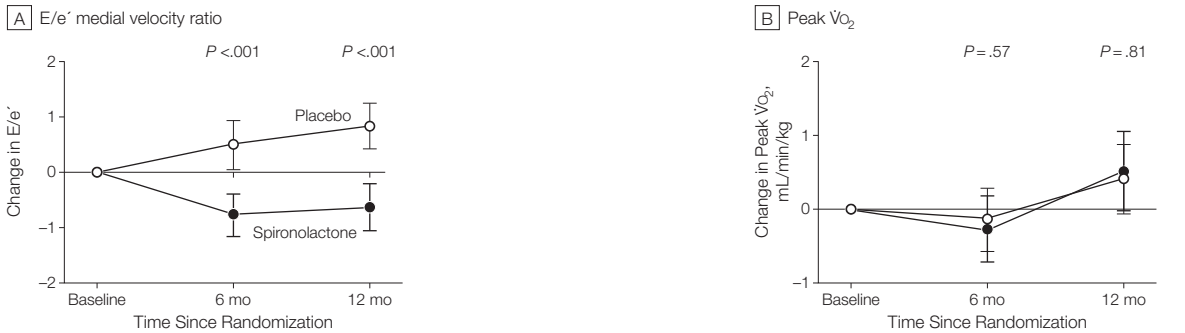
mg). Baseline characteristics were similar between treatment groups (TABLE 1, TABLE 2, and eTable 1).

Primary End Points

Spironolactone significantly improved diastolic function compared with placebo (FIGURE 2A). E/e' significantly declined with spironolactone from 12.7 (SD, 3.6) to 12.1 (SD, 3.7) and increased in the placebo group from 12.8 (SD, 4.4) to 13.6 (SD, 4.3) ($P < .001$ for difference between groups). As shown in Figure 2A, this effect was evident at 6 months and was maintained at 12 months.

Peak $\dot{V}O_2$ increased from 16.3 (SD, 3.6) mL/min/kg to 16.8 (SD, 4.6) mL/min/kg in the spironolactone group and from 16.4 (SD, 3.5) mL/min/kg to 16.9 (SD, 4.4) mL/min/kg in the placebo

Figure 2. Equally Ranked Co–Primary End Points of Peak Early Transmitral Ventricular Filling Velocity to Early Diastolic Tissue Doppler Velocity (E/e') and Peak Oxygen Consumption ($\dot{V}O_2$) According to Assigned Study Treatment



Placebo			
No. of patients	209	196	195
Mean E/e´ (95% CI)	12.8 (12.2-13.4)	13.2 (12.4-13.9)	13.6 (13.0-14.2)
Spironolactone			
No. of patients	213	206	203
Mean E/e´ (95% CI)	12.7 (12.2-13.2)	11.9 (11.5-12.4)	12.1 (11.6-12.6)

Placebo			
No. of patients	209	187	187
Mean peak $\dot{V}O_2$ (95 % CI), mL/min/kg	16.4 (15.9-16.9)	16.4 (15.8-17.0)	16.9 (16.2-17.9)
Spironolactone			
No. of patients	213	194	187
Mean peak $\dot{V}O_2$ (95 % CI), mL/min/kg	16.4 (15.9-16.8)	16.0 (15.5-16.6)	16.8 (16.2-17.5)

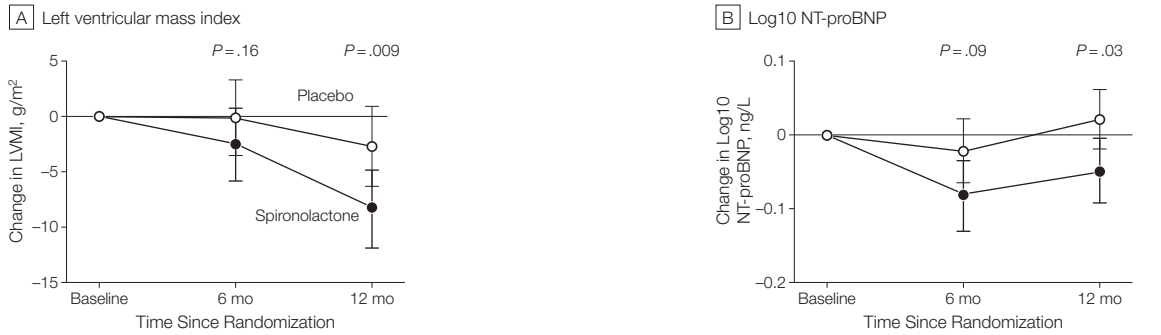
Error bars indicate 95% CI. *P* values describe comparisons of the changes in the placebo or spironolactone group at the respective time point vs baseline. No further improvement by spironolactone occurred between the 6-month and 12-month visits ($P = .39$ for E/e').

Table 3. Echocardiography Results After 12 Months

Measurements	Placebo Group (n = 195)[a]	Spironolactone Group (n = 203)[a]	Spironolactone − Placebo[b] Difference (95% CI)	*P* Value
Primary echocardiographic end point				
E/e' (medial) velocity ratio	13.6 (13.0-14.2)	12.1 (11.6-12.6)	–1.5 (–2.0 to –0.9)	<.001
Secondary end points				
E-wave velocity, cm/s	73.6 (70.6-76.7)	70.5 (68.3-72.7)	–2.5 (–4.9 to –0.2)	.03
Medial e' wave velocity, cm/s	5.86 (5.65-6.06)	6.16 (5.94-6.37)	0.36 (0.13 to 0.60)	.002
E/A velocity ratio	0.96 (0.91-1.01)	0.91 (0.87-0.96)	–0.04 (–0.09 to 0.01)	.08
Isovolumic relaxation time, ms	88 (85-92)	86 (82-90)	–3 (–8 to 2)	.28
Deceleration time, ms	238 (229-247)	241 (232-249)	6 (–6 to 18)	.32
Grade of diastolic dysfunction, No. (%)[c]				
No diastolic dysfunction	2 (1)	4 (2)	0.63 (0.37 to 1.09)[d]	.10
I	129 (68)	143 (75)		
II	57 (30)	43 (23)		
III	0	1 (<1)		
IV	2 (1)	0		
LV ejection fraction, %	65.9 (64.7-67.0)	67.2 (66.1-68.3)	1.6 (0.1 to 3.1)	.04
LV mass index, g/m^2	106 (102-110)	100 (96-103)	–6 (–10 to –1)	.009
Left atrial volume index, mL/m^2	27.6 (26.5-28.6)	27.5 (26.2-28.8)	–0.4 (–1.5 to 0.8)	.51
Other variables				
LV diameter (end diastolic), mm	46.4 (45.5-47.3)	44.6 (43.7-45.4)	–1.4 (–2.5 to –0.3)	.01
LV diameter (end systolic), mm	26.5 (25.6-27.4)	25.5 (24.6-26.4)	–0.6 (–1.8 to 0.5)	.26

Abbreviations: A, peak atrial transmitral ventricular filling velocity; e', early diastolic tissue Doppler velocity; E, peak early transmitral ventricular filling velocity; LV, left ventricular.
[a] Data are expressed as groupwise mean (95% CI) unless otherwise indicated. Higher values indicate better performance for LV ejection fraction and medial e' wave velocity. Lower values indicate better performance for left atrial volume index, E/e' (medial) velocity ratio, and grade of diastolic dysfunction.
[b] Between-group differences are from analysis of covariance, adjusting for baseline.
[c] Data not measured because of presence of atrial fibrillation: placebo, n=5; spironolactone, n=12.
[d] Odds ratio (95% CI).

Figure 3. Main Secondary End Points According to Assigned Study Treatment



Placebo			
No. of patients	209	195	193
Mean LVMI (95% CI), g/m^2	109 (106-113)	109 (105-113)	106 (102-110)
Spironolactone			
No. of patients	212	206	201
Mean LVMI (95% CI), g/m^2	108 (104-112)	105 (101-109)	100 (96-103)

Placebo			
No. of patients	195	190	191
Mean log10 NT-proBNP (95% CI), ng/L	2.19 (2.13-2.25)	2.17 (2.11-2.24)	2.22 (2.15-2.28)
Spironolactone			
No. of patients	204	204	201
Mean log10 NT-proBNP (95% CI), ng/L	2.22 (2.15-2.28)	2.15 (2.08-2.22)	2.18 (2.11-2.25)

LVMI indicates left ventricular mass index; NT-proBNP, N-terminal pro–brain-type natriuretic peptide. Error bars indicate analysis of covariance estimates of treatment effects within subgroups. *P* values describe comparisons of the changes in the placebo or spironolactone group at the respective time point vs baseline. No further change by spironolactone occurred between the 6-month and 12-month visits (*P* = .16 for LVMI and *P* = .87 for log10 NT-proBNP).

group, without a difference between groups (*P* = .81) (Figure 2B).

Results regarding primary end points were consistent across prespecified subgroups (eFigure 1).

Secondary Echocardiographic End Points

Spironolactone improved major measures of cardiac function and remodeling (TABLE 3). Left ventricular ejection fraction increased while left ventricular end-diastolic diameter and left ventricular mass index decreased significantly in the spironolactone group compared placebo (FIGURE 3A). Other measures of diastolic function or cardiac structure did not differ between groups (Table 3 and eTable 2A), but NT-proBNP levels significantly decreased with spironolactone (Figure 3B and TABLE 4).

Secondary Exercise Performance End Points

Results are shown in TABLE 5 and eTable 2B. The slope of $\dot{V}E/\dot{V}CO_2$ slightly increased, but there were no other significant differences between groups.

Secondary Clinical Outcome End Points

Compared with placebo, spironolactone significantly reduced systolic blood pressure (Table 4 and eFigure 2). Heart failure symptoms assessed by NYHA class (Table 4), quality of life, and depressive symptoms did not differ between groups, whereas 6-minute walking distance slightly decreased in the spironolactone group (eFigure 3). Further clinical variables are shown in eTable 2C.

Safety and Adherence

Safety and adherence data are shown in TABLE 6. 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 (Table 4, eFigure 4, and eFigure 5). A significantly greater proportion of patients randomized to spironolactone experienced potassium serum levels greater than 5.0 mmol/L (Table 6), 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* = .003 for intolerance; *P* = .03 for dose reduction) and an increase of potassium serum levels to greater than 5.0 mmol/L (*P* < .001) during follow-up were significantly associated with subjective intolerance or reduction or stopping of the study medication.

Loss to Follow-up

Analyses to examine the possible effects of missing data (eg, last observation carried forward or multiple imputation) did not alter the results on the primary end points (eTable 4).

COMMENT

We evaluated the effect of adding spironolactone to recommended standard risk factor control in patients with HF with preserved EF. We found that left ventricular end-diastolic filling,[24] left ventricular remodeling, and neurohumoral activation were improved with spironolactone, whereas maximal exercise capacity and quality-of-life measures remained unchanged.

Similar reverse remodeling effects of spironolactone have been detected in patients with HF with reduced EF,[25,26] a condition in which spironolactone treatment also reduces all-cause mortality and heart failure hospitalizations.[10,12] Interestingly, it does not improve peak $\dot{V}O_2$ or quality of life in this population.[10,12,27,28] In a recent meta-analysis of 1575 patients with HF with reduced EF, aldosterone antagonists improved NYHA functional status by only 0.13 class, an effect size our study was not powered to detect.[29] Whether mineralocorticoid receptor antagonists may also improve

prognosis in HF with preserved EF is currently being investigated in the international TOPCAT trial.[30]

Activation of the mineralocorticoid receptor system by aldosterone promotes hypertension, endothelial dysfunction, left ventricular hypertrophy, and myocardial fibrosis.[8,9] Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers 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).[31] Spironolactone has been shown to decrease extracellular matrix turnover and myocardial collagen content, mechanisms known to influence the progression of heart failure.[26,32,33]

Aldo-DHF is the first large, multicenter trial to demonstrate structural reverse cardiac remodeling in patients with symptomatic HF with preserved EF treated in addition to substantial antineuroendocrine background therapy

Table 4. Clinical and Laboratory Results and Quality of Life After 12 Months

Measurements	Placebo Group (n = 196)[a]	Spironolactone Group (n = 204)[a]	Spironolactone − Placebo[b] Difference (95% CI)	*P* Value
Clinical secondary end point	(n = 185)	(n = 186)		
Six-minute walk distance, m	536 (521-550)	517 (504-531)	−15 (−27 to −2)	.02
Other clinical variables				
NYHA class, No. (%)				
I	11 (6)	8 (4)	1.30 (0.70 to 2.40)[c]	.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)[c]	.15
Systolic blood pressure, mm Hg	137 (135-139)	128 (126-130)	−8 (−11 to −5)	<.001
Diastolic blood pressure, mm Hg	80 (79-82)	77 (75-78)	−3 (−5 to −2)	<.001
Heart rate, /min	65 (63-66)	66 (65-68)	1 (−1 to 3)	.56
Laboratory secondary end point				
NT-proBNP, median (IQR), ng/L	165 (82-314)	152 (77-307)	0.86 (0.75 to 0.99)[d]	.03
Other laboratory measurements				
Sodium, mmol/L	140.4 (140.0-140.8)	139.5 (139.0-139.9)	−0.9 (−1.4 to −0.5)	<.001
Potassium, mmol/L	4.14 (4.08-4.20)	4.38 (4.32-4.43)	0.2 (0.1 to 0.3)	<.001
Hemoglobin, g/dL	13.8 (13.6-14.0)	13.6 (13.4-13.7)	−0.2 (−0.4 to −0.1)	.003
eGFR, mL/min/1.73 m^2	74 (71-77)	69 (66-71)	−5 (−8 to −3)	<.001
Quality-of-life secondary end points	(n = 187)	(n = 194)		
Minnesota Living With Heart Failure Questionnaire total score	21 (18-23)	21 (19-24)	0.0 (−2 to 2)	.97
SF-36 Physical Functioning Scale score	66 (63-69)	64 (61-68)	1 (−2 to 4)	.62
SF-36 Global Self-Assessment score	3.3 (3.2-3.4)	3.3 (3.2-3.4)	0.0 (−0.1 to 0.1)	.79
Symptoms of depression (PHQ-9 summary score)	5.6 (5.0-6.2)	5.5 (4.9-6.1)	−0.1 (−0.7 to 0.5)	.72
HADS anxiety score	5.0 (4.5-5.6)	4.7 (4.2-5.3)	−0.4 (−0.9 to 0.1)	.14
HADS depression score	4.7 (4.2-5.3)	4.4 (3.8-4.9)	−0.5 (−1.0 to 0.0)	.07

Abbreviations: eGFR, estimated glomerular filtration rate calculated by the Modification of Diet in Renal Disease formula: 186 × (serum creatinine [in micromoles per liter]/88.4)−1.154 × age (in years)−0.203 × 1.21 (if patient is black) × 0.742 (if patient is female); HADS, Hospital Anxiety and Depression Scale; NT-proBNP, N-terminal pro–brain-type natriuretic peptide; NYHA, New York Heart Association; PHQ-9, 9-item depression scale of the Patient Health Questionnaire; SF-36, 36-Item Short Form Health Survey.
[a] Data are expressed as groupwise mean (95% CI) unless otherwise indicated. Higher values indicate better performance for 6-minute walk distance, NYHA class, eGFR, SF-36 Physical Functioning Scale, and SF-36 Global Self-Assessment. Lower values indicate better performance for NT-proBNP, Minnesota Living With Heart Failure Questionnaire total score, symptoms of depression (PHQ-9 summary score), HADS anxiety score, and HADS depression score.
[b] Between-group differences are from analysis of covariance, adjusting for baseline.
[c] Odds ratio (95% CI).
[d] Geometric mean ratio (95% CI).

Table 5. Cardiopulmonary Exercise Testing Results After 12 Months

Measurements	Placebo Group, Mean (95% CI) (n = 187)[a]	Spironolactone Group, Mean (95% CI) (n = 187)[a]	Spironolactone − Placebo[b] Difference (95% CI)	*P* Value
Primary spiroergometric end point				
Peak $\dot{V}O_2$, mL/min/kg	16.9 (16.2-17.5)	16.8 (16.2-17.5)	0.1 (−0.6 to 0.8)	.81
Secondary end points				
$AT\dot{V}O_2$, mL/min/kg	12.1 (11.6-12.6)	11.9 (11.3-12.4)	0.3 (−1.0 to 0.4)	.39
$\dot{V}E/\dot{V}CO_2$ slope	31.5 (30.8-32.2)	31.8 (31.2-32.5)	0.8 (0 to 1.5)	.04
Borg scale	4.6 (4.3-4.9)	4.6 (4.3-4.9)	0.1 (−0.3 to 0.5)	.40
Other variables				
Duration of exercise, s	547 (520-574)	540 (512-567)	10 (−8 to 28)	.27

Abbreviations: $AT\dot{V}O_2$, oxygen consumption at anaerobic threshold; $\dot{V}CO_2$, volume of expired carbon dioxide; $\dot{V}E$, expired volume per unit time; $\dot{V}O_2$, oxygen consumption.
[a] Higher values indicate better performance for duration of exercise, peak $\dot{V}O_2$, and $AT\dot{V}O_2$. Lower values indicate better performance for $\dot{V}E/\dot{V}CO_2$ slope and Borg scale.
[b] Between-group differences are from analysis of covariance, adjusting for baseline.

for risk factor control. Earlier pharmacologic interventions in HF with preserved EF have failed to improve diastolic dysfunction, the major underlying cardiac pathophysiology in HF with preserved EF. Angiotensin receptor blockers[34] and β-blockers[35] have not induced either functional or clinical outcome improvements[3,4] in randomized trials. Hence, spironolactone is the first drug to show an improvement in diastolic function among patients with HF with preserved EF in a randomized, double-blind, placebo-controlled clinical trial.[36] However, we did not observe a reduction in left atrial size as in another recent trial of patients with HF with preserved EF.[37] This may be explained by the mild symptoms and only mildly dilated left atria as well as by the low prevalence of atrial fibrillation in our study. Another explanation could be that functional and structural changes induced by spironolactone need more time to affect left atrial size. In addition, a mild potassium-sparing diuretic effect may have contributed to our findings.

Compared with placebo, spironolactone resulted in a substantial blood pressure reduction, which could explain structural and functional cardiac effects. 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; $P<.001$) and left ventricular mass index (−4.8 g/m^2; 95% CI, −9.4 to −0.3 g/m^2; $P=.04$) remained statistically significant, suggesting that the reverse remodeling effects of spironolactone are independent of blood pressure reduction. However, blood pressure is an indirect measure of left ventricular afterload and correction for blood pressure reduction may not be adequate to refute a primary effect of changes in systolic and diastolic load. Although the mean blood pressure reduction by spironolactone in the Aldo-DHF trial was 5 mm Hg 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 measures.[34] Similarly, enalapril[38] and nebivolol[35] decreased blood pressure without effects on diastolic function or structural remodeling in HF with preserved EF.

Table 6. Adverse Events and Adherence

Events/Adherence	Placebo Group, No. (%)	Spironolactone Group, No. (%)	*P* Value
Adverse events			
Death	0	1 (<1)	>.99
Hospitalization	50 (24)	60 (28)	.38
Cardiac hospitalization	15 (7)	21 (10)	.38
Noncardiac hospitalization	37 (18)	47 (22)	.27
Worsening dyspnea	32 (15)	33 (15)	>.99
New or worsening edema	44 (21)	35 (16)	.26
Worsening coronary heart disease[a]	29 (14)	33 (15)	.68
Myocardial infarction	3 (1)	5 (2)	.72
Worsening renal function[b]	43 (21)	77 (36)	<.001
eGFR <30 mL/min/1.73 m^2 at last visit	1 (<1)	3 (1)	.62
New or worsening anemia[c]	18 (9)	34 (16)	.03
Anemia at last visit	20 (10)	33 (15)	.08
Serum potassium level			
Ever increased >5.0 mmol/L	22 (11)	44 (21)	.005
>5.0 mmol/L at last visit	7 (3)	13 (6)	.25
Ever increased >5.5 mmol/L	3 (1)	4 (2)	>.99
>5.5 mmol/L at last visit	1 (<1)	1 (<1)	>.99
Gynecomastia	1 (<1)	9 (4)	.02
Adherence to study medication			
Overall adherence rate, mean (95% CI), %	93 (91-96)	92 (89-95)	.44
Ever reported intolerance	13 (6)	36 (17)	<.001
Ever reduced dose or stopped	30 (14)	48 (23)	.03

Abbreviation: eGFR, estimated glomerular filtration rate calculated by Modification of Diet in Renal Disease formula: 186 × (serum creatinine [in micromoles per liter]/88.4)−1.154 × age (in years)−0.203 × 1.21 (if patient is black) × 0.742 (if patient is female).

[a] Worsening coronary heart disease is defined as myocardial infarction, revascularization, or occurrence of angina pectoris at follow-up.

[b] Worsening renal function is defined as worsening as reported by the physician, decrease of eGFR to below 30 mL/min/1.73 m^2, or decrease of eGFR by more than 15 mL/min/1.73 m^2 vs baseline.

[c] New or worsening anemia is defined as newly diagnosed anemia according to World Health Organization criteria or worsening of hemoglobin levels in anemic patients by 1 g/dL or more during follow-up.

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, for observing a translation of improved diastolic function into a clinical benefit. The low event rate in the Aldo-DHF trial may indicate that the study population likely represented early-stage HF with preserved EF, and longer follow-up may have been needed to fully evaluate the potential effects of spironolactone on symptomatic or clinical outcome end points. Also, the observed 2.8% reduction in submaximal exercise capacity in the spironolactone group warrants consideration. Although 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. The neutral effect of spironolactone on peak $\dot{V}O_2$ and the small negative effect on 6-minute walking distance could possibly also be explained by a reduction in filling pressures. However, the known antiandrogenic action of spironolactone, with adverse effects on skeletal muscle function and strength independent of myocardial function and left ventricular remodeling, might also have contributed to the lack of symptomatic improvement in our cohort.[39] However, whether a more specific mineralocorticoid receptor blockade using, for instance, eplerenone or canrenone may

result in different outcomes is currently unknown.[13] Nevertheless, the lack of meaningful beneficial effects of spironolactone on various measures of exercise capacity and quality of life suggests that in addition to left ventricular structural and functional remodeling, other mechanisms also contribute to impaired functional capacity in HF with preserved EF.[40]

Spironolactone increased potassium levels by an average of 0.2 mmol/L. Of note, clinically relevant hyperkalemia (>5.5 mmol/L) was rare, potassium levels never exceeded 5.8 mmol/L, and no hospitalizations for hyperkalemia occurred. Observational data after the publication of the RALES study in HF with reduced EF have shown that inappropriately high doses of spironolactone and less rigorous control of risk factors for hyperkalemia in daily practice may shift the risk-benefit ratio of spironolactone toward harm.[38] 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.[40-42] However, at later stages, patients with HF with preserved EF more often die of noncardiovascular causes. Therefore, an intervention with an effect on cardiac structure and function at an earlier phase of the disease as tested in Aldo-DHF seems attractive.[42-44] However, the relatively stable study population 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.

Additionally, in contrast to large outcome trials, NT-proBNP was not selected as a specific inclusion criterion in the Aldo-DHF trial. The reason for this was that NT-proBNP is not a sensitive diagnostic marker of the disease, is influenced by typical comorbidities such as renal dysfunction and obesity, and is not elevated beyond diagnostic cutoff values even in many patients included in large multicenter trials such as I-Preserve.[3] The lack of considerably elevated NT-proBNP levels in Aldo-DHF may indicate a relatively stable HF population, which accounts for the low rate of cardiovascular events observed in our cohort. Because of our study design, typical comorbidities were underrepresented in Aldo-DHF.

To date, there is no accepted minimal clinically important difference in peak $\dot{V}O_2$ or E/e' that should be reached in view of altering prognosis in HF with preserved EF. Future studies, while remaining stringent from a pathophysiologic point of view, need to establish the effect of changes in our echocardiographic and clinical end points on morbidity and mortality.

In conclusion, Aldo-DHF showed that compared with placebo, spironolactone treatment in patients with HF with preserved EF improved diastolic function and left ventricular remodeling but did not alter maximal exercise capacity. The lack of accepted minimal clinically important differences in E/e' or peak $\dot{V}O_2$ in HF with preserved EF warrants additional prospective, randomized, adequately powered studies to further evaluate the effect of improving diastolic function on symptomatic, functional, and clinical end points.

Author Affiliations: Department of Cardiology and Pneumology, Heart Center (Drs Edelmann, Wachter, Duvinage, Stahrenberg, Durstewitz, and Hasenfuss), German Center for Cardiovascular Research (Drs Edelmann, Wachter, Herrmann-Lingen, and Hasenfuss), and Department of Psychosomatic Medicine and Psychotherapy (Dr Herrmann-Lingen), University of Göttingen, Göttingen, Germany; Department of Cardiology, Medical University Graz (Drs Schmidt, Kraigher-Krainer, Colantonio, and Pieske) and Ludwig- Boltzmann Institute for Translational Heart Failure Research (Drs Kraigher-Krainer and Pieske), Graz, Austria; Department of Internal Medicine, MediClin Rehabilitation Center Spreewald, Spreewald, Germany (Dr Kamke); Institute of Medical Informatics, Statistics, and Epidemiology (Dr Löffler) and Clinical Trial Center, University of Leipzig (Dr Gelbrich), Leipzig, Germany; Department of Internal Medicine–Cardiology, Charité–Campus Virchow-Klinikum (Dr Düngen), and Department of Cardiology and Pneumology, Charité–Campus Benjamin Franklin, Universitätsmedizin (Dr Tschöpe), Berlin, Berlin, Germany; Department of Preventive and Rehabilitative Sports Medicine, Technical University Munich, Munich, Germany (Dr Halle); and Institute of Clinical Epidemiology and Biometry, University of Würzburg, Würzburg, Germany (Dr Gelbrich).

Author Contributions: Dr Gelbrich had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Edelmann and Wachter contributed equally to the article and share first authorship.

Study concept and design: Edelmann, Wachter, Schmidt, Löffler, Hermann-Lingen, Halle, Hasenfuss, Gelbrich, Pieske.

Acquisition of data: Edelmann, Wachter, Schmidt, Kraigher-Krainer, Colantonio, Kamke, Duvinage, Stahrenberg, Durstewitz, Düngen, Tschöpe, Halle, Pieske.

Analysis and interpretation of data: Edelmann, Wachter, Schmidt, Kraigher-Krainer, Colantonio, Durstewitz, Düngen, Halle, Hasenfuss, Gelbrich, Pieske.

Drafting of the manuscript: Edelmann, Wachter, Löffler, Pieske.

Critical revision of the manuscript for important intellectual content: Edelmann, Wachter, Schmidt, Kraigher-Krainer, Colantonio, Kamke, Duvinage, Stahrenberg, Durstewitz, Löffler, Düngen, Tschöpe, Hermann-Lingen, Halle, Gelbrich.

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Online-Only Material: The eAppendix, eTables 1 through 4, and eFigures 1 through 5 are available at http://www.jama.com.

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