



Effects of alagebrium, an advanced glycation endproduct breaker, on exercise tolerance and cardiac function in patients with chronic heart failure

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Aims

Advanced glycation endproducts (AGEs) have been associated with the development and progression of chronic heart failure (CHF). Advanced glycation endproducts-crosslink breakers might be of benefit in HF, but only small-scale and uncontrolled data are available. Our aim was to conduct a prospective, randomized, double-blind, placebo-controlled study to examine the effects of the AGE-breaker alagebrium on exercise capacity and cardiac function in patients with HF.

Methods and results

One hundred and two patients with HF (78% male, aged 62 ± 11 years), and a left ventricular ejection fraction (LVEF) ≤ 0.45 , were randomized to either 200 mg alagebrium twice daily or placebo. After 36 weeks, the primary efficacy end-point peak VO_2 had changed by (mean \pm SEM) -2.1 ± 0.5 mL/min/kg in alagebrium vs. -0.5 ± 0.7 mL/min/kg in placebo-treated patients ($P = 0.06$). No significant changes were observed in a number of secondary end-points, including diastolic function (mean E' : $P = 0.32$; E/E' : $P = 0.81$), systolic function (LVEF: $P = 0.43$), AGE accumulation (skin-autofluorescence: $P = 0.42$), N-terminal pro brain natriuretic peptide, $P = 0.20$); New York Heart Association functional class ($P = 0.73$), patient global assessment ($P = 0.32$), physicians global assessment ($P = 0.76$), and the Minnesota Living with Heart Failure Questionnaire score ($P = 0.38$). Overall alagebrium was reasonably well tolerated.

Conclusion

In the present proof-of-concept study, the AGE-breaker alagebrium did not improve exercise tolerance in patients with HF and systolic dysfunction, and no changes were observed in a number of secondary endpoints. The present data therefore do not support earlier data which suggested a beneficial effect of alagebrium in systolic HF. Clinical Trial Registration Information: NCT00516646 (<http://clinicaltrials.gov>)

Keywords

Alagebrium • Advanced glycation endproducts • Heart failure • AGE-crosslink breakers • Aerobic capacity

Introduction

Chronic heart failure (CHF) may occur in the presence of a preserved or depressed left ventricular ejection fraction (LVEF).¹ Both in patients with systolic and diastolic HF, diastolic dysfunction is present and related to symptoms.^{2–5} Even though diastolic

dysfunction is common and strongly related to symptoms, there is a poor understanding of its pathophysiology.⁶ Several mechanisms underlying diastolic HF have been proposed.^{7–11} A potential explanation might be that diastolic dysfunction is related to structural modifications of the extracellular matrix by advanced glycation endproducts (AGEs).^{7,12} Advanced glycation endproduct

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accumulation occurs during life, but increased levels of AGEs are found in patients with diabetes, renal dysfunction, and hypertension. Accumulation of AGEs causes complex vascular as well as myocardial structural and functional changes via the interaction with AGE-receptors, leading to diastolic dysfunction.⁷

Advanced glycation endproduct crosslink breakers might be able to reverse structural changes that are related to diastolic dysfunction. Efficacy of AGE-crosslink breakers in HF is supported by experimental work^{13–16} and two small open-label and uncontrolled clinical studies.^{17,18} In 23 elderly patients with diastolic HF, 210 mg alagebrium twice daily given open-label for 16 weeks reduced left ventricular mass and improved diastolic function.¹⁷ In another open-label study, 35–420 mg alagebrium improved diastolic function and left ventricular remodelling in 20 patients with systolic HF, although these results have only been published as an abstract.¹⁸ Based on the pathophysiological mechanism, supported by small open-label and uncontrolled clinical studies, we initiated a prospective, randomized, double-blind, placebo-controlled study on the effects of the AGE-breaker alagebrium on exercise capacity and cardiac function in patients with systolic HF.

Methods

Patients and study design

The BENEFICIAL (A double-blind, placebo-controlled, randomized trial evaluating the efficacy and safety of Alagebrium (ALT-711) in patients with chronic heart failure) trial is a prospective, randomized, double-blind, placebo-controlled, phase II study evaluating the efficacy and safety of alagebrium (ALT-711) in patients with CHF. The design and baseline characteristics of the BENEFICIAL trial have been published elsewhere.¹⁹ Patients were recruited from the University Medical Center Groningen, and three other regional affiliated hospitals. Inclusion and exclusion criteria are described in detail elsewhere.¹⁹ Briefly, patients with New York Heart Association (NYHA) II–IV stable HF for at least 3 months and a LVEF ≤ 0.45 were eligible for the study. Main exclusion criteria were the inability of patients to undergo exercise testing, cardiac resynchronization therapy, pacemaker therapy, active and/or treated malignancies within 12 months prior to inclusion, and clinically significant renal disturbance. A total of 205 patients were screened for the study (Figure 1). One hundred and three patients were excluded. Main reasons for exclusion were LVEF > 0.45 ($n = 51$), not able to perform a peak VO_2 ($n = 19$), technically insufficient echocardiographic image quality ($n = 8$), not in clinical stable condition ($n = 8$), ischaemia on cardiopulmonary aerobic capacity testing ($n = 7$), and other ($n = 10$). The remaining 102 patients with stable HF were randomized to either 200 mg alagebrium twice daily or placebo for a period of 36 weeks. A 200 mg twice daily dosage was chosen as this has shown efficacy in previous trials using alagebrium in HF.^{17,18} No evidence exists that would support the use of higher dosages. Before randomization, a first rehearse cardiopulmonary aerobic capacity test was performed during a preceding visit to familiarize the patient with the procedures. Efficacy measurements, including cardiopulmonary aerobic capacity testing and echocardiography, were performed at baseline, and at 36 weeks. After randomization, safety visits were made at 12 week intervals. In addition, extra safety visits were made 2 weeks after randomization, and 4 weeks after study medication was stopped. Recruitment started November 2007 and was completed at the end of December 2008. The study was approved by the Medical Ethical Committee and all subjects gave written informed consent (NCT00516646).

Randomization and masking

Randomization was done via the use of the interactive voice response system. Randomization data were kept strictly confidential until the time of unblinding. Drug codes were broken and made available for data analysis after the study was completed, and the data file was verified.

Cardiopulmonary aerobic capacity testing

Cardiopulmonary aerobic capacity testing was performed using a CareFusion, Masterscreen CPX (Houten, The Netherlands) according to a modified Bruce protocol, which increases the workload more gradually than the Bruce protocol.²⁰ Oxygen uptake (VO_2), carbon dioxide production (VCO_2), and minute ventilation were measured using breath-by-breath gas analysis. Patients were encouraged to continue exercising until their $\text{VO}_{2\text{-max}}$ was reached, they become uncomfortably symptomatic, or discontinuation was indicated for safety reasons. Peak VO_2 was determined as an average value of the two highest VO_2 values at peak performance, expressed as mL/min/kg, mL/min/fat-free mass, as well as a percentage of predicted peak oxygen consumption. As an indication of the condition of a patient, 50% recovery time, after maximum exercise, was measured (T1/2).

Echocardiography

Echocardiography was performed by experienced cardiac technicians using a General Electric VIVID 7 system (Horton, Norway) with a 2.5–3.5 MHz probe. Measurements included left ventricular and atrial dimensions, peak early (E) and late (A) diastolic filling velocities, isovolumetric relaxation time, and deceleration time (DCT; slope) of the early peak filling. Furthermore, using colour-coded tissue Doppler imaging (ccTDI), early diastolic velocity (E') was measured on the lateral, and septal wall areas, and subsequently averaged. E/E' was calculated by dividing the peak early diastolic filling (E) by the mean E' measured using ccTDI. Systolic dysfunction was determined by calculating Simpson's LVEF. When Simpson LVEF could not be determined, eyeballing LVEF was estimated. Eyeballing LVEF was independently estimated by two experienced cardiac technicians. When no consensus was reached, a third cardiac technician was consulted. In 37 out of 97 patients Simpson's LVEF could not be determined and was estimated by eyeballing LVEF.

Skin-autofluorescence

Tissue AGE accumulation was assessed using a validated skin-autofluorescence (skin-AF) reader (AGE-reader; patent PCT/NL99/00607; DiagnOptics BV, Groningen, The Netherlands), as described previously.^{21,22} In short, the AGE reader illuminates a skin surface of $\sim 2 \text{ cm}^2$, guarded against surrounding light, with an excitation light source between 300 and 420 nm (peak excitation $\sim 370 \text{ nm}$). Light from the skin was measured with a spectrometer in the 420–600 nm range, using 200 μm glass fibre. The value of skin-AF was calculated as the ratio of the light intensity in the 420–600 nm wavelength range, and the light intensity in the 300–420 nm wavelength range.

Endpoints

The primary endpoint of the study was the effect of alagebrium on aerobic capacity measured by cardiopulmonary exercise testing and determined as an average value of the two highest VO_2 values at peak performance expressed as mL/min/kg. Peak VO_2 was also expressed as mL/min/fat free mass as well as a percentage of predicted peak oxygen consumption. In addition to a first rehearse cardiopulmonary aerobic capacity test (used for screening only),

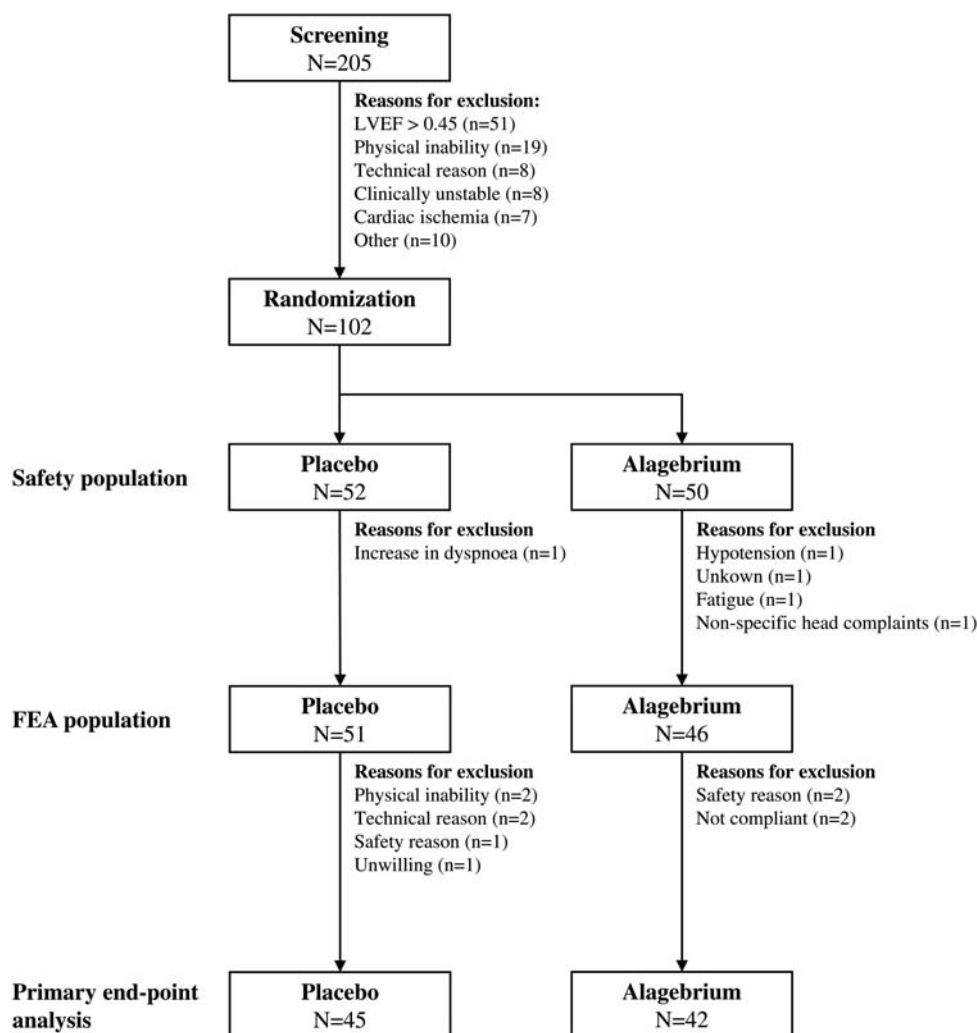


Figure 1 Patient inclusion and exclusion. Figure 1 illustrates patient in- and exclusion. Two hundred and five patients were screened of whom 103 were excluded. Of 102 randomized patients, 5 were not included in the full efficacy analysis (FEA) population. In 10 patients, we were unable to obtain primary end-point follow-up data, leaving 87 patients available for primary end-point efficacy analysis.

cardiopulmonary exercise testing was performed at baseline and after 36 weeks of treatment. Secondary endpoints were diastolic function expressed as change in mean E' and E/E' , systolic function expressed as change in LVEF, AGEs in tissue measured as change in skin-AF, change in Minnesota Living with Heart Failure scores (MLHF), change in NYHA functional class, change in patient's and physician's global assessment scores, and change in levels of N-terminal pro brain natriuretic peptide (NT-proBNP).

Statistical considerations

Sample size calculation

The primary aim was to study the effect of alagebrium (ALT-711) on aerobic capacity. Based on the data of Mancini *et al.*²³ we estimated that an increase of at least 15% in peak VO_2 would be of clinical significance. To demonstrate an increase of 15% in aerobic capacity, with a power of at least 80% at a significance level of 0.05, 78 patients would be needed to study the primary end-point. With an expected drop-out of ~20%, a total of 100 randomized patients would be needed.

Statistical analysis plan

Continuous variables were expressed as mean \pm standard deviation, mean \pm standard error of the mean (SEM), or as median (25–75% interquartile range), where applicable. Nominal variables were expressed as n (%). Efficacy analyses were performed on the full efficacy analysis (FEA) population. Safety analyses were performed on all randomized patients ($n = 102$). The FEA population consisted of all randomized patients who continued medication until at least the 12 week visit. Patients who discontinued at or after the 12 week visit, and could be brought in for efficacy measurements within 2 weeks of stopping study medication, were included in the FEA population. Five patients were excluded from the FEA population because of early discontinuation, leaving 97 patients available for efficacy analyses (Figure 1). The FEA population was used to calculate baseline characteristics (Table 1). Baseline characteristics were analysed for difference over treatment group by using analysis of variance (ANOVA) or Mann–Whitney U test where applicable for continuous variables and by χ^2 for nominal variables. Primary and secondary efficacy analyses on group differences were performed by using ANOVA

Table 1 Baseline characteristics of 97 systolic chronic heart failure patients randomized to alagebrium or placebo

Parameters	Treatment group		P-value
	Placebo (n = 51)	Alagebrium (n = 46)	
Age(years)	59 ± 11	64 ± 11	0.03
Sex (male), n (%)	39 (77)	37 (80)	0.64
Diabetes mellitus, n (%)	7 (14)	10 (22)	0.30
Race (caucasian), n (%)	50 (98)	45 (98)	0.94
History of hypertension, n (%)	15 (29)	17 (37)	0.43
History of hypercholesterolaemia, n (%)	32 (63)	30 (65)	0.80
Smoking, n (%)	12 (24)	11 (24)	0.97
Body mass index (kg/m ²)	28 ± 4	28 ± 4	1.00
Systolic blood pressure (mmHg)	116 ± 16	115 ± 15	0.71
Diastolic blood pressure (mmHg)	74 ± 9	71 ± 9	0.05
Heart rate (bpm)	71 ± 15	66 ± 11	0.06
Aetiology of HF			0.94
Ischaemic, n (%)	33 (65)	35 (76)	
Non-ischaemic, n (%)	18 (35)	11 (24)	
Idiopathic	15 (29)	7 (15)	
Other	3 (6)	4 (9)	
NYHA functional class, n (%)			0.97
II	32 (63)	30 (65)	
III	18 (35)	14 (31)	
IV	1 (2)	2 (4)	
Laboratory assessments			
eGFR (MDRD) (mL/min/1.73 m ²)	79 ± 22	81 ± 20	0.60
NT-proBNP (ng/L)	267 [93–631]	465 [204–964]	0.04
HbA1c (%)	5.7 [5.5–6.0]	5.7 [5.6–6.2]	0.47
Total cholesterol (mmol/L)	4.4 ± 1.0	4.3 ± 1.2	0.84
Skin-AF (a.u.)	2.2 ± 0.5	2.4 ± 0.7	0.20
MLHF questionnaire			
Total score	18 ± 14	23 ± 19	0.14
Physical sub-score	9 ± 6	11 ± 9	0.32
Echocardiography			
E/A	0.9 [0.7–1.1]	0.9 [0.7–1.3]	0.63
Dct (ms)	212 ± 58	217 ± 57	0.71
IVRT (ms)	104 ± 26	99 ± 20	0.41
E/E'	12.1 [10.1–15.5]	14.3 [9.5–21.3]	0.61
Mean E' (cm/s)	5.1 ± 1.8	5.1 ± 2.1	0.95
LVEF	0.33 ± 0.09	0.33 ± 0.09	0.99
LVEDD (mm)	58.7 ± 8.2	58.5 ± 7.9	0.92
LVESD (mm)	48.0 ± 9.7	47.0 ± 10.2	0.63
VO ₂ max exercise test			
Peak VO ₂ (mL/min/kg)	22.5 ± 6.4	21.1 ± 5.8	0.28
Peak VO ₂ (mL/min/kg fat free mass)	33.3 ± 9.2	31.0 ± 7.6	0.18
Peak VO ₂ (% predicted VO ₂ max)	84.4 ± 26.0	86.0 ± 24.6	0.75
Medication use, n (%)			
ACEi/ARB	48 (94)	43 (94)	0.90
β-Blockers	48 (94)	44 (96)	0.73
Diuretics	30 (59)	27 (59)	0.99
Aldosterone antagonists	14 (27)	15 (30)	0.83

Continuous variables are expressed as mean ± standard deviation or as median (25–75% interquartile range), where applicable.

Nominal variables were expressed as n (%).

bpm, beats per minute; HF, heart failure; NYHA, New York Heart Association; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease; NT-proBNP, N-terminal pro brain natriuretic peptide; HbA1c, haemoglobin A1c; Skin-AF, skin autofluorescence; MLHF, Minnesota Living with Heart Failure; DCT, deceleration time; IVRT, isovolumetric relaxation time; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

for normally distributed variables or Mann–Whitney *U* test for skewed distributed variables. For qualitative parameters, group differences were evaluated using a χ^2 test. For subgroup analyses *P* for interaction was calculated using general linear modelling with ANOVA. No attempt was made to replace missing values. All statistical tests were two sided. A *P*-value <0.05 was considered to be statistically significant. Data were analysed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA).

Role of funding source

Synvista therapeutics has had limited influence in study design. Final decisions were made by the principal investigator A.A. Voors. Synvista therapeutics had no influence on data collection, data analysis, interpretation of data, in the writing of the report, and in the decision to submit the paper for publication.

Results

Baseline characteristics of the FEA population stratified according to treatment allocation are depicted in Table 1. Mean age was 62 ± 11 years, 78% of patients were male, 18% were diabetic, and mean systolic blood pressure was 115 ± 15 mmHg. The

study population was generally well balanced, except for a slightly higher age, lower diastolic blood pressure, and higher baseline NT-proBNP levels in the alagebrium group.

Primary end-point efficacy analysis

Results of the primary end-point efficacy analysis are summarized in Table 2 and Figure 2. For various reasons, as illustrated in Figure 1, 10 patients were unable to perform a cardiopulmonary exercise test at 36 weeks, leaving 87 patients available for the primary end-point efficacy analysis. Aerobic exercise capacity measured as peak VO_2 (mL/min/kg) changed by -2.1 ± 0.5 mL/min/kg in alagebrium vs. -0.5 ± 0.7 mL/min/kg in placebo-treated patients ($P = 0.06$ for change between groups). This effect was of similar magnitude when peak VO_2 was expressed in mL/min/kg fat free mass ($P = 0.04$) and as percentage of predicted peak VO_2 ($P = 0.07$). No significant differences were observed for respiratory quotient ($P = 0.37$), anaerobic threshold ($P = 0.69$), and $T_{1/2}$ peak VO_2 ($P = 0.15$).

Secondary end-point efficacy analysis

Results of the secondary end-point efficacy analysis are summarized in Table 3. No significant differences were observed in changes in mean E' ($P = 0.32$), E/E' ($P = 0.81$), LVEF ($P = 0.43$), skin-AF ($P = 0.42$), NT-proBNP ($P = 0.20$), NYHA functional class (0.73), patient global assessment ($P = 0.32$), physicians global assessment ($P = 0.76$), and MLHF score ($P = 0.38$). Although left ventricular end-diastolic diameter (LVEDD) and left ventricular end-systolic diameter (LVESD) were not defined as a pre-specified secondary end-point they were evaluated to establish whether the use of alagebrium was associated with changes in left

Table 2 Primary end-point efficacy analysis

Parameters	Treatment group		<i>P</i> -value
	Placebo (<i>n</i> = 45)	Alagebrium (<i>n</i> = 42)	
Peak VO_2 (mL/min/kg)			
Baseline	22.5 ± 1.0	21.4 ± 0.9	
Follow-up	22.1 ± 0.9	19.4 ± 0.8	
Difference	-0.5 ± 0.7	-2.1 ± 0.5	0.06
Peak VO_2 (mL/min/kg fat free mass)			
Baseline	33.3 ± 1.4	31.2 ± 1.2	
Follow-up	33.1 ± 1.4	28.3 ± 1.1	
Difference	-0.2 ± 1.0	-2.9 ± 0.7	0.04
Peak VO_2 (% predicted)			
Baseline	85.4 ± 3.9	87.2 ± 3.9	
Follow-up	83.7 ± 3.2	80.0 ± 3.7	
Difference	-1.7 ± 2.4	-7.3 ± 1.9	0.07
Respiratory quotient			
Baseline	1.06 ± 0.02	1.08 ± 0.02	
Follow-up	1.08 ± 0.02	1.08 ± 0.02	
Difference	0.02 ± 0.02	0.00 ± 0.01	0.37
Anaerobic threshold (mL/min/kg)			
Baseline	13.2 ± 0.5	12.8 ± 0.4	
Follow-up	13.8 ± 0.5	13.1 ± 0.5	
Difference	0.6 ± 0.5	0.3 ± 0.4	0.69
$T_{1/2}$ peak VO_2 (seconds)			
Baseline	94 ± 6	98 ± 6	
Follow-up	94 ± 5	108 ± 6	
Difference	0 ± 5	11 ± 6	0.15

Variables were expressed as mean \pm SEM.

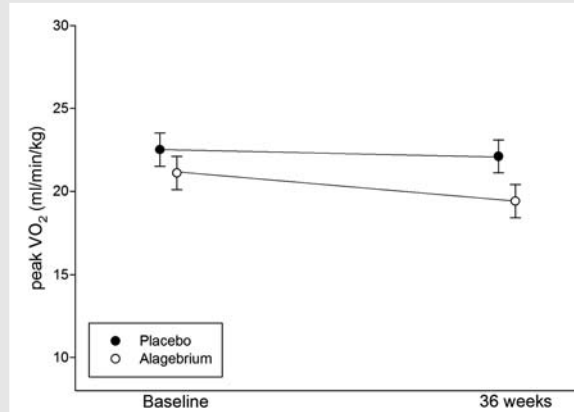


Figure 2 Changes in peak oxygen uptake (VO_2) stratified according to treatment group. Figure 2 illustrates the results of the primary end-point efficacy analysis. Mean peak oxygen uptake values at baseline as well as at the 9-month visit are shown. Error bars indicate standard error of the means. Aerobic exercise capacity measured as peak oxygen uptake (mL/min/kg) changed from 22.5 ± 1.0 to 22.1 ± 0.9 mL/min/kg in placebo- and from 21.4 ± 0.9 to 19.4 ± 0.8 mL/min/kg in alagebrium-treated patients ($P = 0.06$ for change between groups).

Table 3 Secondary end-point efficacy analysis

Parameters	Treatment group		P-value
	Placebo (n = 51)	Alagebrium (n = 46)	
Mean E' (cm/s)			
Baseline	5.2 ± 0.3	5.1 ± 0.3	0.32
Follow-up	5.2 ± 0.3	4.7 ± 0.4	
Difference	0.0 ± 0.2	−0.3 ± 0.3	
E/E'			
Baseline	13.6 ± 1.0	17.1 ± 1.8	0.81
Follow-up	12.9 ± 1.2	16.8 ± 1.6	
Difference	−0.7 ± 1.0	−0.2 ± 1.7	
LVEF			
Baseline	0.33 ± 0.01	0.33 ± 0.01	0.43
Follow-up	0.34 ± 0.02	0.32 ± 0.02	
Difference	0.01 ± 0.01	−0.01 ± 0.01	
Skin-AF (a.u.)			
Baseline	2.2 ± 0.1	2.3 ± 0.1	0.42
Follow-up	2.1 ± 0.1	2.2 ± 0.1	
Difference	−0.1 ± 0.1	−0.2 ± 0.1	
NT-proBNP (ng/L)			
Baseline	267 [93–631]	465 [204–964]	0.20
Follow-up	246 [101–800]	407 [198–936]	
Difference	8 [−60–159]	−14 [−220–97]	
NYHA functional class (%)			0.73
Baseline			
II	32 (63)	30 (65)	
III/IV	19 (37)	16 (35)	
Follow-up			
I/II	40 (82)	33 (75)	
III/IV	9 (18)	11 (25)	
Patient global assessment (score)			
Cumulative score ^a	0.7 ± 0.2	0.4 ± 0.2	0.32
Physicians global assessment (score)			
Cumulative score ^a	0.5 ± 0.2	0.5 ± 0.2	0.76
MLHF questionnaire (total score)			
Baseline	18 ± 2	21 ± 3	0.38
Follow-up	18 ± 2	25 ± 3	
Difference	1 ± 2	3 ± 2	
MLHF questionnaire (physical sub-score)			
Baseline	9 ± 1	10 ± 1	0.21
Follow-up	9 ± 1	11 ± 1	
Difference	0 ± 1	1 ± 1	

Continuous variables were expressed as mean ± SEM or as median (25–75% interquartile range), where applicable. Nominal variables are expressed as n (%).

NYHA, New York Heart Association; Skin-AF, skin autofluorescence; NT-proBNP, N-terminal pro brain natriuretic peptide; MLHF, Minnesota Living with Heart Failure; LVEF, left ventricular ejection fraction.

^aPatient and physicians global assessment were scored per follow-up visit as much worse (−2), worse (−1), stable (0), better (1), and much better (2). Cumulative score was used for analyses.

ventricular dimensions. No end-diastolic dilatation was observed in the alagebrium-treated patients (*P*-value for within group analysis: *P* = 0.35). Left ventricular end-diastolic diameter changed from (mean ± SEM) 58.7 ± 1.2 to 56.8 ± 1.1 mm in placebo- and 58.7 ± 1.3 to 59.4 ± 1.3 mm in alagebrium-treated patients

(*P*-value for between-group analysis: *P* = 0.01). Left ventricular end-systolic diameter changed from (mean ± SEM) 48.0 ± 1.4 to 46.3 ± 1.4 mm in placebo- and 47.4 ± 1.7 to 48.6 ± 1.7 mm in alagebrium-treated patients (*P*-value for between-group analysis: *P* = 0.03; *P*-value for within-group analysis: *P* = 0.26).

Subgroup analyses

Pre-specified subgroup analyses were performed for subgroups defined by diabetes, age, aetiology of CHF, NYHA functional class, gender, peak VO_2 , LVEF, mean E' , E/E' , NT-proBNP, and skin-AF. Results of subgroup analyses are summarized in *Figure 3*. No significant interaction was observed.

Safety analysis

Safety analyses were performed on all randomized patients ($n = 102$). In total nine patients discontinued treatment, of which six were using alagebrium. Reasons for discontinuation in alagebrium-treated patients were symptomatic hypotension ($n = 1$), and unwilling to further participate without clear reason ($n = 5$). Reasons for discontinuation in placebo-treated patients were ventricular arrhythmias ($n = 1$), and unwilling to further participate without clear reason ($n = 2$). Serious adverse events (SAEs) and adverse events (AEs) are summarized in *Table 4*. In total 41 SAEs were reported of which 20 were in alagebrium-treated patients. One patient in the alagebrium group died as a consequence of lung cancer. Lung cancer was diagnosed shortly after the patient completed the study protocol. No differences in incidence rates were observed for death and/or hospitalizations. In total 319 AEs were reported of which 175 were in alagebrium-treated patients. Alagebrium-treated patients more often had gastrointestinal symptoms ($P = 0.02$).

Discussion

The present study is the first report of a placebo-controlled study on the effects of an AGE-crosslink breaker in HF. Advanced glycation endproducts have been proposed as an important mechanism in HF.^{7,12} Advanced glycation endproducts are carbohydrate- and lipid-dependent modifications of protein, formed by oxidative or non-oxidative reactions. They affect the physiological properties of proteins in the extracellular matrix, such as charge, hydrophobicity, turnover, and elasticity. The latter is caused by an important mechanism of AGEs, the formation of collagen crosslinks, which results in increased myocardial stiffness. Secondary to that, AGEs cause complex vascular as well as myocardial structural and functional changes via the interaction with AGE-receptors. The deleterious effect of AGEs can be targeted in several ways, of which the use of AGE-crosslink breakers has shown to be most promising.

The AGE-crosslink breaker alagebrium has been examined for several indications, including hypertension, peripheral vascular disease, and HF both in experimental settings as well as clinical studies. Alagebrium has been shown to improve endothelial function,²⁴ arterial compliance,²⁵ and diastolic function.^{17,18} In 23 elderly patients with diastolic HF, 210 mg alagebrium twice daily given open-label for 16 weeks reduced left ventricular mass and improved diastolic function. Patients participating in this trial had diastolic HF and an LVEF above 0.50, while we included patients with an ejection fraction ≤ 0.45 . Of note, this study was open label and did not have a control group. In another open-label and uncontrolled study, 35–420 mg alagebrium improved diastolic

function and left ventricular remodelling in 20 patients with systolic HF, although these results have only been published as an abstract.¹⁸

Despite a strong background and rationale, the AGE-crosslink breaker alagebrium did not improve exercise capacity or cardiac function in the current study. The selection of our patient population could have influenced our findings. Although patients with systolic dysfunction frequently have diastolic dysfunction as well, we did not specifically select patients with diastolic dysfunction, in whom the largest effect of alagebrium could be expected. Additionally, we observed a small trend towards a more pronounced negative treatment effect of alagebrium in patients with low LVEFs in subgroup analysis. One could argue that we should have chosen a diastolic dysfunction group who were more likely to benefit from AGE breaker therapy. Although we agree that the rationale for AGE breaker therapy is stronger for patients with diastolic HF, the rationale was also strong for its use in systolic HF. Not only because most patients with systolic dysfunction also have a markedly deteriorated diastolic dysfunction, but also because AGE-breaking therapy has shown to improve vascular function and could thereby decrease afterload. Secondly, tissue AGE levels were relatively low in our population, with only very few diabetic patients, and therefore the contribution of AGE-crosslinks to their impaired exercise capacity might have been negligible. Third, the duration of treatment might have been too short to induce a clinical impact in this population. Finally, despite a scientific rationale that AGEs play a role in the pathophysiology of HF, AGE-crosslink breakers might not be the appropriate therapy to interfere with this process.

After 36 weeks of treatment, LVEDD remained unchanged in the alagebrium group, while it decreased in the placebo group. Similar findings were observed for LVESD. From a pathophysiological perspective one may hypothesize that AGE-breaking therapy reduces AGE-crosslinks, thus increasing left ventricular compliance and inducing left ventricular dilatation. Evidence does exist that alagebrium therapy is associated with aortic dilatation in elderly hypertensive dogs, but left ventricular properties in this study remained unaffected.²⁶ Also, in the aforementioned small clinical studies^{17,18} no increase in left ventricular end-diastolic volume was observed.

We performed a pre-specified subgroup analysis to investigate whether the effects of AGE-breaking therapy would be more pronounced in certain subgroups. We expected to find a more pronounced effect of AGE-breaking therapy in the older, diabetic patients with worse diastolic function and high baseline AGE levels. However, no such significant interactions were observed. A possible explanation for this unexpected result could be the low number of patients with these specific features, especially with respect to the low number of patients with diabetes.

Advanced glycation endproduct accumulation was measured by skin-AF. No treatment effect of alagebrium was found on skin-AF. One can question whether to expect a treatment effect, since it is unknown how AGE-crosslink breakers influence circulating and tissue AGE levels.

Generally, alagebrium appeared to be safe and well tolerated. We found no increases in the incidence of death and/or

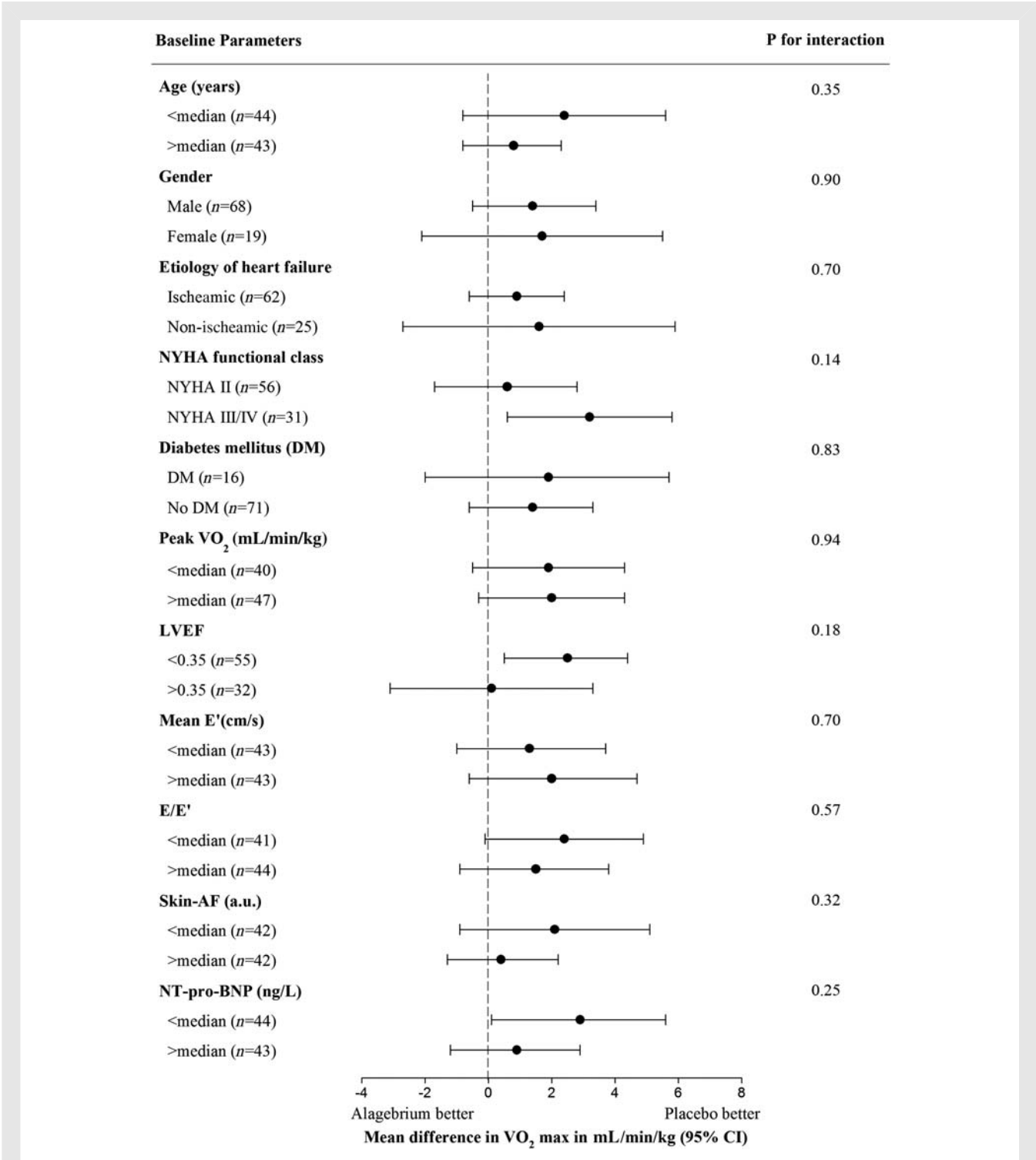


Figure 3 Pre-specified subgroup analysis. Figure 3 illustrates the results of the pre-specified subgroup analysis. Means \pm 95% confidence intervals are shown. Specific subgroup means were calculated by subtracting mean oxygen uptake (VO₂) max (mL/min/kg) in alagebrium-treated patients from mean oxygen uptake max in placebo-treated patients. P for interaction was calculated using general linear modelling with analysis of variance.

hospitalizations, and the use of alagebrium was associated with only a small increase in gastrointestinal symptoms. However, the trend towards a small decrease in exercise tolerance and the increase in LVEDD found in this study is potentially of concern. It should, however, be noted that LVEDD was not a predefined endpoint of this study.

Table 4 Safety results

Parameters	Treatment group		P-value
	Placebo (n = 52)	Alagebrium (n = 50)	
Serious adverse events			
Death	0 (0)	1 (2)	0.31
All-cause hospitalizations	20 (38)	21 (42)	0.72
Cardiovascular hospitalizations	12 (23)	10 (20)	0.71
ICD implantations/replacements	3 (6)	4 (8)	0.66
Other	5 (10)	7 (14)	0.49
Adverse events			
Cardiovascular			
Rhythm disturbances	7 (13)	14 (28)	0.07
Fatigue	11 (21)	13 (26)	0.57
Dyspnoea	7 (13)	11 (22)	0.26
Blood pressure fluctuation	4 (8)	9 (18)	0.12
Cardiac failure	3 (6)	9 (18)	0.06
Chest pain	1 (2)	5 (10)	0.08
Dizziness	4 (8)	8 (16)	0.19
Malaise	3 (6)	5 (10)	0.43
Gastrointestinal	8 (15)	18 (36)	0.02
Musculoskeletal	19 (37)	10 (20)	0.06
Respiratory	18 (35)	12 (24)	0.24
Urogenital	6 (12)	10 (20)	0.24
Other	53	51	

Limitations

Our study population consisted of well-treated HF patients with relatively low NT-proBNP levels at baseline, probably related to the selection of patients that were able to undergo exercise testing. Therefore, severely symptomatic patients, very elderly patients, and those with serious co-morbidities, limiting their exercise capacity were less likely to be included in this study. Results can therefore not be readily applied to more severely symptomatic HF patients. Also, although we feel that our study was adequately powered, it remains a phase II study with a small number of patients. Finally, although the large majority of patients with systolic HF also have severe diastolic dysfunction, these findings cannot be translated to patients with HF with a preserved ejection fraction.

Conclusions

In the present proof-of-concept study, the AGE-breaker alagebrium, did not improve exercise tolerance in patients with HF and systolic dysfunction, and no changes were observed in a number of secondary endpoints. The present data therefore do not support earlier data which suggested a beneficial effect of alagebrium in systolic HF patients.

Conflict of interest: The University Medical Center Groningen will receive royalties of possible future net sales of alagebrium.

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