

Effects of alagebrium, an advanced glycation end-product breaker, in patients with chronic heart failure: study design and baseline characteristics of the BENEFICIAL trial

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Aims

Previous small open label studies have shown that the advanced glycation end-product (AGE) breaker alagebrium may improve cardiac function in patients with chronic heart failure (HF). We report the design, methods and baseline characteristics of a double-blind, placebo-controlled, randomized trial evaluating the efficacy and safety of alagebrium (BENEFICIAL) in patients with HF and a left ventricular ejection fraction (LVEF) ≤ 0.45 .

Methods and results

Patients with NYHA II–IV stable HF for at least 3 months were eligible for this study. One hundred and two patients were included in the study and randomized to either 200 mg alagebrium twice daily or placebo for a period of 36 weeks. The mean age of patients was 60 ± 11 years, 78% were male, and 17% were diabetic. Mean peak VO_2 was 21.7 ± 5.9 mL/min/kg, mean LVEF was 0.32 ± 0.09 . Diastolic function was worse (mean early tissue diastolic velocity (E') 4.6 ± 1.7 vs. 6.1 ± 2.0 cm/s; $P < 0.001$) in patients with LVEF ≤ 0.35 compared to patients with LVEF between 0.35 and 0.45.

Conclusion

The BENEFICIAL study is a proof-of-concept study that will provide new data on the efficacy and safety of the AGE crosslink breaker alagebrium in systolic HF patients. EudraCT number of this trial is NCT00516646.

Keywords

Heart failure • Advanced glycation end-products • AGE breaker

Introduction

Chronic heart failure (HF) may occur in the presence of a preserved or depressed left ventricular ejection fraction (LVEF).^{1,2} Patients with HF with a preserved ejection fraction (diastolic HF) have decreased ventricular relaxation, abnormal active relaxation, and/or an increase in ventricular and arterial stiffness.^{2–4} Patients with a depressed ejection fraction (systolic HF) have an abnormal contraction pattern, but the majority of these patients also have diastolic dysfunction.^{3,4} In fact, diastolic function is even more impaired in patients with systolic HF compared to patients with diastolic HF.⁵ Importantly, in patients with systolic HF, diastolic function, and not systolic function, is related to NYHA HF class

and predicts exercise intolerance measured with cardiopulmonary exercise testing.⁶

Even though diastolic dysfunction is common and strongly related to symptoms, there is no standardized treatment to improve diastolic function.^{7–9} Previous studies have shown no clear beneficial effect with angiotensin-receptor blockers (ARBs) or angiotensin-converting enzyme (ACE) inhibitors on clinical outcome in patients with diastolic HF,^{10–13} although a recent sub-study from SENIORS showed that nebivolol may possibly be equally effective in elderly patients with HF with either preserved or impaired ejection fraction.¹⁴ We currently lack HF agents specifically targeted at improving diastolic function. A potential explanation might be that diastolic dysfunction is related to

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structural modifications of the extracellular matrix, which can be prevented, but not reversed by ACE-inhibitors, ARBs, or beta-blockers.

Advanced glycation end-product (AGE)-crosslink breakers might be able to reverse the structural changes that are related to diastolic dysfunction (Figure 1). AGEs are end-products formed by oxidative or non-oxidative reactions between sugars and proteins often referred to as the Maillard reaction.¹⁵ AGEs form excessive crosslinks in the extracellular matrix, which may induce myocardial diastolic dysfunction and hypertension.^{15–18} Circulating AGEs have been correlated with vascular compliance in humans and may therefore also induce vascular stiffening.¹⁹ Diastolic, systolic, and vascular dysfunction may cause decreased exercise capacity (Figure 1). Therefore, it seems reasonable to believe that AGE-crosslink breakers might improve diastolic function and exercise capacity in patients. This is supported by small and open label studies with alagebrium in patients with diastolic dysfunction.^{17,20} In the DIAMOND trial, 210 mg alagebrium twice daily (b.i.d.) given open-label for 16 weeks reduced left ventricular mass and improved diastolic function in 23 elderly patients with diastolic HF.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.²⁰

Based on the pathophysiological mechanism, supported by small open-label clinical studies, we hereby report the design, methods, and baseline characteristics of a prospective, randomized, double-blind, placebo controlled trial on the effects of the AGE-breaker

alagebrium on exercise capacity and diastolic function in 102 patients with systolic HF.

Methods

Patients and study design

BENEFICIAL is a prospective, randomized, double-blind, placebo-controlled, phase II study evaluating the efficacy and safety of alagebrium (ALT-711) in patients with HF.

Patients were recruited from the University Medical Center Groningen, the Martini Hospital Groningen, the Refaja Hospital Stadskanaal, and Ommelander Hospital Group location Delfzicht, The Netherlands.

Inclusion and exclusion criteria are described in Table 1. In brief, patients with NYHA II–IV stable HF for at least 3 months and

Table 1 Inclusion and exclusion criteria for the BENEFICIAL trial

Inclusion criteria

- NYHA II–IV heart failure
- Echocardiographic ejection fraction ≤ 0.45
- HF duration of at least 3 months
- Stable HF medical therapy for at least 1 month
- Patients able to understand the study procedures and willing to provide informed consent

Exclusion criteria

- Patient aged ≤ 18 years
- History of myocardial infarction in previous 6 months
- History of stroke/TIA/RIND in previous 6 months
- Severe valvular dysfunction
- Severe pulmonary disease
- History of systemic inflammatory or collagen vascular disease
- Active and/or treated malignancies within 12 months prior to inclusion
- Any significant condition either medical or non-medical that could lead to difficulty complying with the protocol
- Patients on cardiac resynchronization therapy (CRT) or scheduled for CRT implantation
- Pacemaker therapy (unless rescue pacing at ≤ 40 b.p.m.) or scheduled pacemaker implantation
- History of valve replacement or surgery
- Uncontrolled diabetes (HbA1c $> 9.5\%$)
- Clinically significant renal dysfunction (sMDRD calculated $\text{GFR} \leq 30 \text{ mL/min/1.73 m}^2$)
- Clinically significant liver function abnormalities (ASAT/ALAT > 2.5 times the upper limit of normal)
- Severe anaemia at baseline (haemoglobin $< 10 \text{ g/dL}$ or $< 6.2 \text{ mmol/L}$)
- Use of any investigational drug(s) within 30 days prior to screening
- Pregnancy or active breast-feeding (pregnancy tests will be performed on all female subjects of child-bearing potential)
- Active pericarditis/myocarditis
- Patients unable to undergo exercise testing

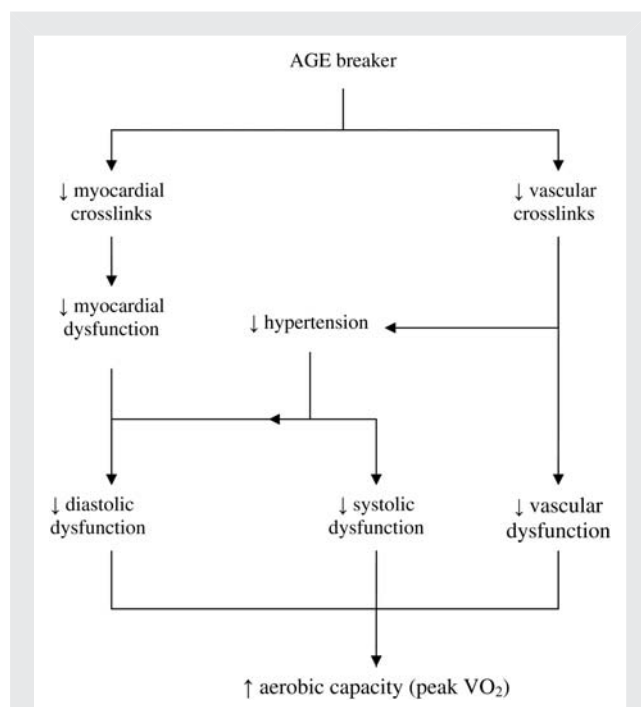


Figure 1 Schematic representation of the pathophysiological pathways by which the advanced glycation end-product breaker alagebrium increases aerobic capacity.

NYHA, New York Heart association; HF, heart failure; MDRD, modification of diet in renal disease; GFR, glomerular filtration rate; TIA, transient ischaemic attack; RIND, reversible ischaemic neurological deficit; ASAT, aspartate amino transferase; ALAT, alanine amino transferase.

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 dysfunction.

The study schedule is depicted in Figure 2. Patients were randomized to either alagebrium 200 mg b.i.d. or placebo for a period of 36 weeks. Before randomization, a practice cardiopulmonary aerobic capacity test was performed to familiarize the patient with the procedure. Efficacy measurements were performed at baseline, and at the end of the study, and included physical examination, cardiopulmonary aerobic capacity testing (peak VO_2), echocardiography, Minnesota Living with Heart Failure score, AGE measurements in tissue and in blood, NYHA HF class, patient's and physician's global assessment, and NT-pro-BNP levels. After randomization, safety visits were performed at 12-week intervals. In addition, one safety visit was performed 2 weeks after the randomization visit and another 4 weeks after study treatment had stopped. At all visits except at the visit to practice the peak VO_2 test, blood pressure, heart rate, skin-autofluorescence (skin-AF; a validated non-invasive method to study tissue AGEs²¹) were measured, an ECG performed and blood drawn for laboratory analysis. The estimated glomerular filtration rate was calculated using the modification of diet in renal disease (MDRD) formula.²² Patient's and physician's global assessments were performed at each visit. Recruitment started in November 2007 and was completed at the end of December 2008. The study was approved by the appropriate Medical Ethics Committee and all subjects gave written informed consent.

Skin-autofluorescence

Tissue AGE accumulation was assessed using a validated skin-AF reader (AGE-reader; patent PCT/NL99/00607; DiagnOptics BV, Groningen, The Netherlands), as described previously.²¹ In short, the AGE reader illuminates an area of skin surface of approximately 2 cm², which is protected from the surrounding light, with an excitation light source between 300–420 nm (peak excitation ~ 370 nm). Light from the skin is measured with a spectrometer in the 420–600 nm range, using 200 μm glass fibre. The value of skin-AF is 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. Skin-AF was measured at the volar side of the lower arm at approximately 10–15 cm below the elbow fold. The measurement was performed three times at a healthy skin site (i.e. without visible vessels, scars, or other skin abnormalities) and an average was calculated.

Echocardiography

Two-dimensional echocardiography was performed at the screening visit and at the end of the study²³ by experienced cardiac technicians using a General Electric VIVID 7 system with a 2.5–3.5-MHz probe. Measurements included left ventricular and atrial dimensions. Diastolic function was measured with peak early (E) and late (A) diastolic filling velocities, isovolumetric relaxation time, deceleration time of the early peak filling. Early diastolic tissue velocity (E') was measured on the lateral and septal wall areas, using colour-coded tissue Doppler imaging (TDI). E/E' was calculated by dividing the peak early diastolic filling (E) by the average E' . Diastolic dysfunction was defined as a mean $E' < 8$ cm/s and/or an $E/E' > 10$. Systolic dysfunction was determined by Simpson's LVEF and defined as a LVEF ≤ 0.45 . If Simpson's LVEF could not be determined, LVEF was estimated visually.

Cardiopulmonary aerobic capacity testing

Cardiopulmonary aerobic capacity testing was performed according to the Modified Bruce protocol, which increases the workload more gradually than the Bruce protocol. The first stage was performed at 1.7 mph and 0% grade, the second stage at 1.7 mph and 5% grade, and the third stage corresponds to the first stage of the Bruce protocol.²⁴ Each exercise test started with an acclimatization period standing on the treadmill. A standard 12-lead electrocardiogram was recorded continuously during exercise testing. Blood pressure was recorded at regular intervals using a manual cuff sphygmomanometer. Patients were encouraged to continue the exercise until either their peak VO_2 was reached, they became 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. Oxygen uptake (VO_2), carbon dioxide production (VCO_2), and minute ventilation were measured using breath-by-breath gas analysis.

Endpoints

The primary endpoint of the study is 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.²⁵ Peak VO_2 will also be determined as ml/min/fat-free mass as well as a percentage of predicted peak oxygen consumption. Secondary endpoints are: (i) diastolic function measured by TDI; (ii) LVEF measured with echocardiography; (iii) AGEs in tissue measured with skin-AF and in blood measured with mass spectrometry analysis; (iv) quality of life measured with Minnesota Living with Heart Failure score; (v) NYHA

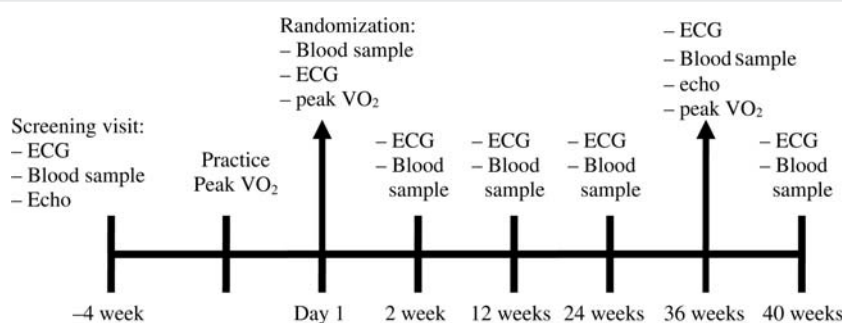


Figure 2 Study schedule. ECG, electrocardiogram; peak VO_2 cardiopulmonary aerobic capacity test.

HF class; (vi) patient's and physician's global assessment scores; and (vii) NT-pro-BNP levels.

Statistical considerations

Sample size calculation

The primary aim is to study the effect of alagebrium (ALT-711) on aerobic capacity. According to data from Mancini *et al.*,²⁶ the expectation is that an increase of at least 15% in peak VO_2 is clinically significant. In the Mancini study, peak VO_2 increased significantly from 11 ± 0.8 to 12.7 ± 2.8 mL/min/kg. 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 objective. With an expected drop-out of 20%, a total of 100 randomized patients will have to be included.

Statistical analysis plan

For safety parameters, all randomized patients who received at least one dose of the study drug will be included in the safety analysis and analysed according to the treatment they actually received. The efficacy analysis will be carried out on the full efficacy analysis (FEA) population. The FEA population consists of all patients who have a baseline measurement and continued medication until at least the 12-week visit. Patients who discontinued before the 12-week visit will not be included in the FEA population. If a patient discontinues at or after the 12-week visit, and can be brought in for assessment within two weeks of stopping study medication, the full 36-week efficacy dataset will be collected and used. All statistical tests will be two-sided. A *P*-value of less than 0.05 is considered to be statistically significant. Missing data will remain missing, and no attempt will be made to replace missing values. The primary endpoint is the absolute change from baseline of the aerobic capacity (peak VO_2) at exercise testing. The effect on the primary and key secondary endpoints will be summarized for subgroups defined by diabetes, age (median), aetiology of HF (ischaemic vs. non-ischaemic), NYHA functional class (II vs. III and IV), gender, peak VO_2 , LVEF ≤ 0.35 vs. LVEF > 0.35 , mean E' , E/E' , NT-pro-BNP, and skin-AF. For quantitative parameters, overall group differences will be evaluated using an *F*-test for

normally distributed variables or a Kruskal–Wallis test for variables with a skewed distribution. For qualitative parameters, overall group differences will be evaluated using a χ^2 test.

Interim analysis

Following randomization of 30 subjects, an interim analysis on the safety of the study drug in the study population will be performed by an independent data safety monitoring board. Investigators remain blinded. Furthermore, safety will be assessed by summarizing incidence and type of adverse events during the study period. All patients will be included in the safety assessment.

Results

A total of 205 patients were screened for the study. One hundred and three patients were excluded (Figure 3). 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 a clinically stable condition ($n = 8$) and ischaemia on cardiopulmonary aerobic capacity testing ($n = 7$). A total of 102 patients with stable HF were thus included in the study. Baseline characteristics of the study population are depicted in Table 2. The mean age of patients was 60 ± 11 years, 78% were male, 17% diabetic, and the mean systolic blood pressure was 115 ± 15 mmHg. Mean skin-AF was 2.3 ± 0.6 a.u., and mean peak VO_2 was 21.7 ± 5.9 mL/min/kg, which is 84% of the predicted values for patients with similar age and gender. The average calculated early diastolic velocity measured on the lateral and septal wall areas was 5.2 ± 1.9 cm/s, the median E/E' was 12.7 (10.0–18.3). Mean LVEF was 0.32 ± 0.09 . The median NT-pro-BNP level was 403 (154–851) ng/L. Patients were well treated, 94% of the patients used an ACE-inhibitor or an ARB and 93% a beta-blocker.

An important predefined subgroup analysis will be performed on patients with an LVEF ≤ 0.35 ($n = 61$) and an LVEF between

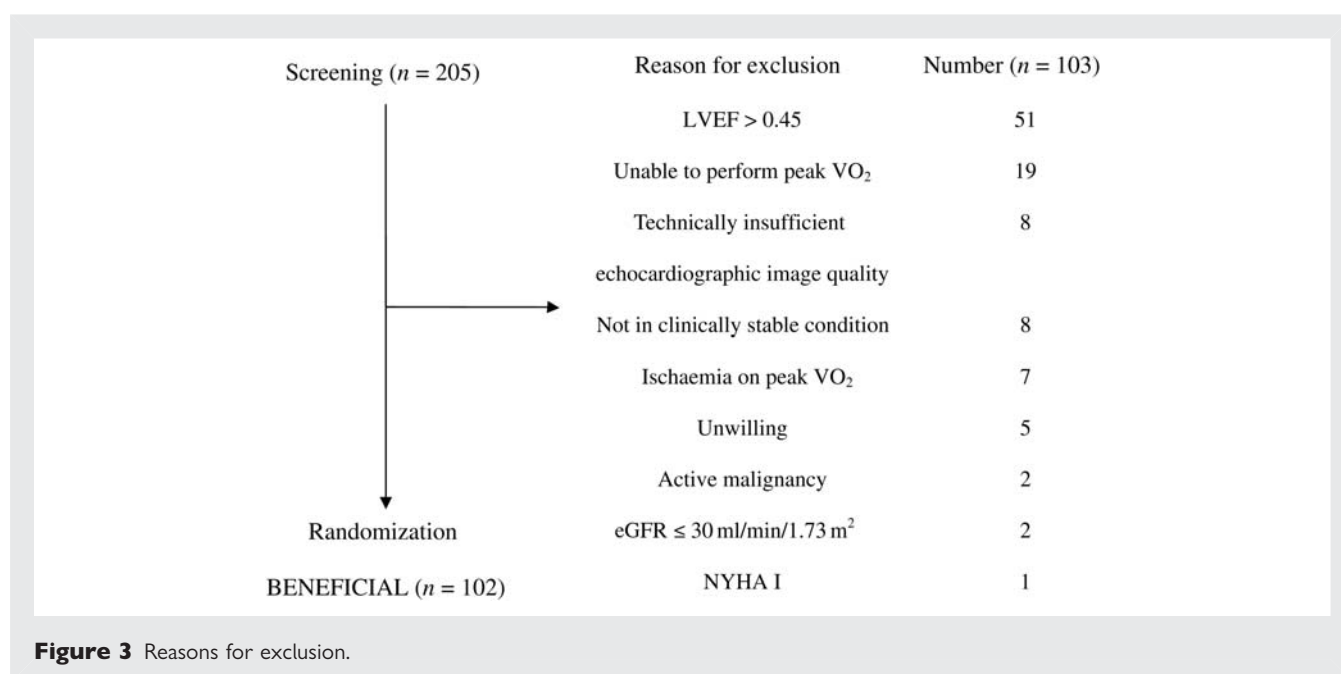


Table 2 Baseline clinical characteristics of patients

Variables	All patients (n = 102)	LVEF ≤ 35% (n = 61)	LVEF > 35% (n = 41)	P-value
Age (years)	60 ± 11	61.0 ± 10.8	59.6 ± 12.1	0.54
Sex (male), n (%)	80 (78)	50 (82)	30 (73.2)	0.29
Diabetes, n (%)	17 (17)	14 (23)	3 (7.3)	0.04
Race (Caucasian), n (%)	100 (98)	59 (96.7)	41 (100)	0.24
History of hypertension, n (%)	32 (31.4)	21 (34.4)	11 (26.8)	0.42
Smoking, n (%)				0.19
None	15 (14.7)	8 (13.1)	7 (17.1)	
Current	22 (21.6)	16 (26.2)	6 (14.6)	
Past	65 (63.7)	37 (60.7)	28 (68.3)	
History of hypercholesterolaemia, n (%)	58 (56.9)	36 (59)	22 (53.7)	0.59
Body mass index (kg/m ²)	28 ± 4.3	28.4 ± 4.4	27.3 ± 4.0	0.20
Systolic blood pressure (mmHg)	115 ± 15	115.9 ± 15.8	113 ± 14.3	0.72
Heart rate (b.p.m.)	69.5 ± 14.3	69 ± 12.3	70.1 ± 17.0	0.39
Aetiology of HF, n (%)				0.03
Ischaemic	70 (68.6)	47 (77)	23 (56.1)	
Non-ischaemic	32 (31.4)	14 (23)	18 (43.9)	
NYHA functional class, n (%)				0.97
II	66 (64.7)	40 (65.6)	26 (63.4)	
III	33 (32.4)	18 (29.5)	15 (36.6)	
IV	3 (2.9)	3 (4.9)	0 (0)	
Laboratory assessments				
eGFR (mL/min/1.73 m ²)	79.9 ± 20.8	75.6 ± 19.6	81.9 ± 22.6	0.43
NT-pro-BNP (ng/L)	403 (154–851)	486 (215–990)	243 (93–567)	0.01
HbA1c (%)	5.7 (5.5–6.2)	5.8 (5.6–6.3)	5.6 (5.4–5.9)	0.03
Total cholesterol (mmol/L)	4.4 ± 1.1	4.3 ± 1.2	4.5 ± 0.99	0.28
Skin-AF (a.u.)	2.3 ± 0.6	2.3 ± 0.62	2.1 ± 0.59	0.08
MLHF	18 (7.0–29.8)	18 (7–29)	18 (7–30)	0.79
Echocardiography				
E/A	0.89 (0.69–1.17)	0.85 (0.65–1.20)	0.93 (0.81–1.15)	0.20
Dct (ms)	217.8 ± 57.7	215 ± 63.4	214.4 ± 48.4	0.96
IVRT (ms)	101.6 ± 23.6	104.8 ± 26.0	96.4 ± 18.0	0.07
E/E'	12.7 (10–18.3)	14.1 (11.2–20.5)	11.0 (9.0–13.7)	0.001
Mean E' (cm/s)	5.2 ± 1.9	4.6 ± 1.7	6.1 ± 2.0	<0.001
LVEF	0.32 ± 0.09	0.26 ± 0.07	0.40 ± 0.03	<0.001
Peak VO ₂ (mL/min/kg)	21.7 ± 5.9	20.4 ± 4.9	23.5 ± 7.4	0.02
Percentage of predicted peak VO ₂	84 ± 24	79.9 ± 20.5	90.7 ± 30.2	0.05
Medication use, n (%)				
ACE-inhibitors/ARB	96 (94)	59 (97)	37 (90)	0.18
Beta-blockers	95 (93)	58 (95)	37 (90)	0.35
Diuretics	56 (55)	40 (66)	20 (49)	0.09
Aldosterone antagonists	29 (28)	20 (33)	9 (22)	0.24

NYHA, New York Heart Association; MDRD, modification of diet in renal disease; NT-pro-BNP, N-terminal-pro-brain natriuretic peptide; MLHF, Minnesota Living with Heart Failure; Dct, deceleration time; IVRT, isovolumetric relaxation time; LVEF, left ventricular ejection fraction; ACE-i, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; skin-AF, skin-autofluorescence.

0.35 and 0.45 ($n = 41$). Table 2 demonstrates that patients with an $\text{LVEF} \leq 0.35$ were more often diabetic (14 vs. 3; $P = 0.04$) and more often had an ischaemic aetiology of HF (47 vs. 23; $P = 0.03$). Importantly, these patients had more severe HF, as reflected by a lower peak VO_2 (20.4 ± 4.9 vs. 23.5 ± 7.4 mL/min/kg; $P = 0.02$), higher median NT-proBNP levels (486 (215–990) vs. 243 (93–567) pg/mL; $P = 0.01$), and worse diastolic

function (mean early tissue diastolic velocity (E') 4.6 ± 1.7 vs. 6.1 ± 2.0 cm/s; $P < 0.001$).

Discussion

AGE-breakers might become a novel treatment modality for patients with HF.²⁷ The aim of the BENEFICIAL study is to evaluate

the efficacy and safety of the AGE-breaker alagebrium on aerobic capacity and diastolic function in patients with HF.

We chose to include patients with a decreased LVEF ($\text{LVEF} \leq 0.45$) for two major reasons. First, we aimed to study the effects of alagebrium in a wide range of HF patients, but since this is a small study, we needed to decrease the risk of including non-HF patients. Therefore, patients should have a clear diagnosis of HF with clear signs of systolic dysfunction. In addition, a subgroup analysis will be performed in patients with $\text{LVEF} \leq 0.35$ and in patients with LVEF between 0.35 and 0.45. Second, diastolic function is even more impaired in patients with a reduced LVEF, when compared to patients with a preserved LVEF. This is supported by data from our study, in which patients with $\text{LVEF} \leq 0.35$ had a worse diastolic function than patients with $\text{LVEF} > 0.35$. Interestingly, in patients with HF and a reduced LVEF, diastolic dysfunction (and not systolic function) has been shown to be related to NYHA HF class and to predict exercise intolerance.^{5,6} This is a direct result of an increase in left ventricular diastolic pressures and pulmonary venous pressures during exercise in patients with diastolic dysfunction. Therefore, it seems reasonable to believe that exercise intolerance in patients with systolic HF is largely driven by associated abnormal left ventricular diastolic function.

Skin-AF was used as a non-invasive measure for skin autofluorescence to assess tissue AGE accumulation. In this population, mean skin-AF was 2.3 ± 0.6 a.u. To our knowledge this is the first report of tissue AGE accumulation in patients with HF. Mean age at baseline was 60 years. Furthermore, in this study population 85% of patients are current smokers or were smokers in the past, 31% have hypertension and 17% have diabetes. It is known that AGE accumulation is related to these risk factors.²⁸

Expected results and potential clinical implications

Increased AGEs cause ventricular and arterial stiffness through the formation of excessive crosslinks in the extracellular matrix (Figure 1). By breaking these collagen crosslinks, AGE-breakers can reverse a process that seems to contribute to diastolic dysfunction. In contrast, ACE-inhibitors and ARBs might prevent collagen formation, but once crosslinking has occurred, they might not be able to reverse this process. This is a potential explanation for the demonstrated inability of ACE-inhibitors and ARBs to improve clinical outcome in HF patients with diastolic dysfunction.^{7,9} Because of their novel and unique mode of action, we believe that AGE-breakers might become a novel therapy to improve clinical outcome in patients with HF. Two small open-label studies with alagebrium have already shown promising effects in HF patients.^{17,20}

Limitations

Two limitations of this study should be addressed. First, this is a relatively small study population, and a relatively large increase in peak VO_2 (15%) is needed to achieve a statistically significant result. Second, baseline aerobic capacity, which was measured with peak VO_2 in the present study, was 21.7 mL/min/kg, which

is higher than expected. In addition, in our subgroup of patients with a $\text{LVEF} \leq 0.35$, mean peak VO_2 was significantly lower than in patients with a $\text{LVEF} > 0.35$, but higher than in previous studies investigating the effect of interventions on exercise capacity.²⁹ The main reasons for this are; the selection of patients able to perform a reasonable cardiopulmonary exercise test, and the stable clinical condition of this very well-treated population. A peak VO_2 of 21.7 mL/min/kg is comparable to that reported in a similar study population by Lapu-Bula *et al.*,³⁰ in which patients with dilated cardiomyopathy had a mean peak VO_2 of 21 mL/min/kg. However, our sample size calculations were based on data from Mancini *et al.* in which peak VO_2 increased significantly from 11 ± 0.8 to 12.7 ± 2.8 mL/min/kg. As previously described, the peak VO_2 of our patients was better than anticipated, although peak VO_2 was still impaired. Therefore, our anticipated improvement of 15% might be optimistic, and it therefore remains to be seen whether the patient numbers are sufficient to detect meaningful changes.

Conclusion

Recent studies both in animals and humans have suggested that AGEs play a role in the development and progression of HF. AGE-breakers have been shown to improve left ventricular diastolic function in small uncontrolled studies.^{17,31} A possible explanation could be that AGE-breakers improve the structural modifications that are caused by accumulation of AGEs. BENEFICIAL is the first prospective randomized placebo-controlled clinical study of an AGE-breaker in HF patients. If an improvement in exercise capacity and diastolic function is shown, this will be a major step towards a new treatment strategy in HF patients.

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

References

1. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Stromberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur J Heart Fail* 2008;**10**:933–989.
2. Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure—abnormalities in active relaxation and passive stiffness of the left ventricle. *N Engl J Med* 2004;**350**:1953–1959.
3. Jessup M, Brozena S. Heart failure. *N Engl J Med* 2003;**348**:2007–2018.
4. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure. Part I: diagnosis, prognosis, and measurements of diastolic function. *Circulation* 2002;**105**:1387–1393.
5. Bursi F, Weston SA, Redfield MM, Jacobsen SJ, Pakhomov S, Nkomo VT, Meverden RA, Roger VL. Systolic and diastolic heart failure in the community. *JAMA* 2006;**296**:2209–2216.

6. Parthenakis FI, Kanoupakis EM, Kochiadakis GE, Skolidis EI, Mezilis NE, Simantirakis EN, Kanakarakaki MK, Vardas PE. Left ventricular diastolic filling pattern predicts cardiopulmonary determinants of functional capacity in patients with congestive heart failure. *Am Heart J* 2000;**140**:338–344.
7. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur Heart J* 2006;**27**:2338–2345.
8. Yip GW, Wang M, Wang T, Chan S, Fung JW, Yeung L, Yip T, Lau ST, Lau CP, Tang MO, Yu CM, Sanderson JE. The Hong Kong diastolic heart failure study: a randomised controlled trial of diuretics, irbesartan and ramipril on quality of life, exercise capacity, left ventricular global and regional function in heart failure with a normal ejection fraction. *Heart* 2008;**94**:573–580.
9. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet* 2003;**362**:777–781.
10. Araujo AQ, Arteaga E, Ianni BM, Buck PC, Rabello R, Mady C. Effect of Losartan on left ventricular diastolic function in patients with nonobstructive hypertrophic cardiomyopathy. *Am J Cardiol* 2005;**96**:1563–1567.
11. Mattioli AV, Zennaro M, Bonatti S, Bonetti L, Mattioli G. Regression of left ventricular hypertrophy and improvement of diastolic function in hypertensive patients treated with telmisartan. *Int J Cardiol* 2004;**97**:383–388.
12. Muller-Brunotte R, Kahan T, Lopez B, Edner M, Gonzalez A, Diez J, Malmqvist K. Myocardial fibrosis and diastolic dysfunction in patients with hypertension: results from the Swedish Irbesartan Left Ventricular Hypertrophy Investigation versus Atenolol (SILVHIA). *J Hypertens* 2007;**25**:1958–1966.
13. Solomon SD, Janardhanan R, Verma A, Bourgoun M, Daley WL, Purkayastha D, Lacourciere Y, Hippler SE, Fields H, Naqvi TZ, Mulvagh SL, Arnold JM, Thomas JD, Zile MR, Aurigemma GP. Effect of angiotensin receptor blockade and antihypertensive drugs on diastolic function in patients with hypertension and diastolic dysfunction: a randomised trial. *Lancet* 2007;**369**:2079–2087.
14. van Veldhuisen DJ, Cohen-Solal A, Bohm M, Anker SD, Babalis D, Roughton M, Coats AJ, Poole-Wilson PA, Flather MD. Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction: data from SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure). *J Am Coll Cardiol* 2009;**53**:2150–2158.
15. Hartog JW, Voors AA, Bakker SJ, Smit AJ, van Veldhuisen DJ. Advanced glycation end-products (AGEs) and heart failure: pathophysiology and clinical implications. *Eur J Heart Fail* 2007;**9**:1146–1155.
16. Hartog JW, Voors AA, Schalkwijk CG, Scheijen J, Smilde TD, Damman K, Bakker SJ, Smit AJ, van Veldhuisen DJ. Clinical and prognostic value of advanced glycation end-products in chronic heart failure. *Eur Heart J* 2007;**28**:2879–2885.
17. Little WC, Zile MR, Kitzman DW, Hundley WG, O'Brien TX, deGroof RC. The effect of alagebrium chloride (ALT-711), a novel glucose cross-link breaker, in the treatment of elderly patients with diastolic heart failure. *J Card Fail* 2005;**11**:191–195.
18. Nielsen JM, Kristiansen SB, Nørregaard R, Andersen CL, Denner L, Nielsen TT, Flyvbjerg A, Botker HE. Blockage of receptor for advanced glycation end products prevents development of cardiac dysfunction in db/db type 2 diabetic mice. *Eur J Heart Fail* 2009;**11**:638–647.
19. Yoshida N, Okumura K, Aso Y. High serum pentosidine concentrations are associated with increased arterial stiffness and thickness in patients with type 2 diabetes. *Metabolism* 2005;**54**:345–350.
20. Thohan V, Koerner MM, Pratt CM, Torre GA. Improvements in diastolic function among patients with advanced systolic heart failure utilizing alagebrium (an oral advanced glycation end-product cross-link breaker). *Circulation* 2005;**112**: Suppl. 2, 2647.
21. Meerwaldt R, Links T, Graaff R, Thorpe SR, Baynes JW, Hartog J, Gans R, Smit A. Simple noninvasive measurement of skin autofluorescence. *Ann NY Acad Sci* 2005;**1043**:290–298.
22. Smilde TD, van Veldhuisen DJ, Navis G, Voors AA, Hillege HL. Drawbacks and prognostic value of formulas estimating renal function in patients with chronic heart failure and systolic dysfunction. *Circulation* 2006;**114**:1572–1580.
23. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA, Evangelista A. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr* 2009;**22**:107–133.
24. Sheffield LT, Roitman D. Stress testing methodology. *Prog Cardiovasc Dis* 1976;**19**:33–49.
25. van den Broek SA, van Veldhuisen DJ, de Graeff PA, Landsman ML, Hillege H, Lie KI. Comparison between New York Heart Association classification and peak oxygen consumption in the assessment of functional status and prognosis in patients with mild to moderate chronic congestive heart failure secondary to either ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 1992;**70**:359–363.
26. Mancini DM, Katz SD, Lang CC, LaManca J, Hudaihed A, Androne AS. Effect of erythropoietin on exercise capacity in patients with moderate to severe chronic heart failure. *Circulation* 2003;**107**:294–299.
27. Kindermann M, Reil JC, Pieske B, van Veldhuisen DJ, Bohm M. Heart failure with normal left ventricular ejection fraction: what is the evidence? *Trends Cardiovasc Med* 2008;**18**:280–292.
28. Hartog JW, de Vries AP, Lutgers HL, Meerwaldt R, Huisman RM, van Son WJ, de Jong PE, Smit AJ. Accumulation of advanced glycation end products, measured as skin autofluorescence, in renal disease. *Ann NY Acad Sci* 2005;**1043**:299–307.
29. Flynn KE, Pina IL, Whellan DJ, Lin L, Blumenthal JA, Ellis SJ, Fine LJ, Howlett JG, Keteyian SJ, Kitzman DW, Kraus WE, Miller NH, Schulman KA, Spertus JA, O'Connor CM, Weinfurt KP. Effects of exercise training on health status in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA* 2009;**301**:1451–1459.
30. Lapu-Bula R, Robert A, De Kock M, D'Hondt AM, Detry JM, Melin JA, Vanoverschelde JL. Relation of exercise capacity to left ventricular systolic function and diastolic filling in idiopathic or ischemic dilated cardiomyopathy. *Am J Cardiol* 1999;**83**:728–734.
31. Asif M, Egan J, Vasani S, Jyothirmayi GN, Masurekar MR, Lopez S, Williams C, Torres RL, Wagle D, Ulrich P, Cerami A, Brines M, Regan TJ. An advanced glycation endproduct cross-link breaker can reverse age-related increases in myocardial stiffness. *Proc Natl Acad Sci USA* 2000;**97**:2809–2813.