Galectin-3 in Heart Failure with Preserved Ejection Fraction – the Effects of Chronic Aldosterone Receptor Blockade (The Aldo-DHF Trial)

K. Durstewitz[1], V. Holzendorf[2], R. Wachter[1], G. Gelbrich[3] , R. Stahrenberg[1], G. Hasenfuß[1], B. Pieske[4], F. Edelmann[1]

1 Department of Cardiology and Pneumology, University of Göttingen, Germany; 2 Coordinating Center for Clinical Trials, University of Leipzig, Germany; 3 Department for Clinical Epidemiology and Biometry, University of Würzburg, Germany; 4 Department of Cardiology, Medical University Graz, Austria;

Background

Galectin-3 and aldosterone are mediators of cardiac fibrosis, ventricular remodeling and adverse outcome in heart failure. The effect of a chronic aldosterone receptor blockade on Galectin-3 in patients with heart failure and preserved ejection fraction (HFPEF) has not been investigated so far.

Methods

The multicenter, randomized, double-blind, placebo-controlled Aldo-DHF (Aldosterone Receptor Blockade in Diastolic Heart Failure) trial included n=422 patients (age 67±8 years, 52% females) with chronic HFPEF (NYHA II/III, LVEF>50%, and echocardiographic evidence of diastolic dysfunction). Patients received 25 mg spironolactone or matching placebo once a day (1:1). The co-primary end points were changes in peak VO_2, and in E/e' at 12 months. Physical examination, echocardiography and spiroergometry were performed and blood samples (NT-proBNP, Galectin-3) were collected at baseline and after 6 and 12 months.

Results

Table 1: Baseline Characteristics
(differences between groups with different Galectin-3 levels)

Variable *n (%), MW (±SD)*	*Total* *n=415*	*Galectin-3* *≤12.1ng/ml* *n=208*	*Galectin-3* *>12.1ng/ml* *n=207*	*p-value*
Demographics				
Age (yrs)	67 (±8)	65 (±7)	68 (±8)	**<0.001**
Female Gender	217 (52.3%)	100 (48.1%)	117 (56.5%)	0.085
Signs and Symptoms of HF				
NYHA III	58 (14.0%)	20 (9.6%)	38 (18.4%)	**0.010**
Edema	164 (39.5%)	68 (32.7%)	96 (46.4%)	**0.004**
Nycturia	334 (80.5%)	159 (76.4%)	175 (84.5%)	**0.037**
Laboratory				
HDL Cholesterol (mg/dl)	57.5 (±15.4)	59.4 (±16.2)	55.5 (±14.3)	**0.011**
Hemoglobin (g/dl)	13.8 (±1.2)	14.0 (±1.1)	13.7 (±1.3)	**0.012**
eGFR (ml/min/1.73m²)	78.7 (±18.7)	84.7 (±17.2)	72.5 (±18.2)	**<0.001**
NT-proBNP (pg/ml)	159 (84-299)	140 (75-225)	192 (93-377)	**<0.001**
Cardiopulmonary Exercise Testing				
Work Load (Watt)	100.1 (±29.2)	104.2 (±29.0)	95.9 (±28.9)	**0.004**
Exercise Duration	541 (±175)	571 (±175)	510 (±170)	**<0.001**
Peak VO2 (ml/kg/min)	16.3 (±3.5)	16.9 (±3.2)	15.8 (±3.6)	**0.001**
AT VO2 (ml/kg/min)	11.6 (±3.2)	12.1 (±3.3)	11.1 (±3.1)	**0.002**
VE/VCO2 Slope	30.3 (±5.2)	29.7 (±5.3)	31.0 (±5.1)	**0.016**
6-Minute-Walk-Test				
Distance (m)	530 (±87)	546 (±83)	514 (±88)	**<0.001**
Echocardiography				
LAVI (ml/m²)	28.1 (±8.5)	27.1 (±7.4)	29.1 (±9.3)	**0.022**
E/e´	12.8 (±4.1)	12.3 (±3.6)	13.2 (±4.4)	**0.023**

Table 2: Association of Galectin-3 levels and indicators of exercise capacity/ echocardiographic indicators of diastolic dysfunction (unadjusted, multiple adjusted)

Values are B-coefficients (95%-CI) by Regression	*Model 1*	*p-value*	*Model 2*	*p-value*	*Model 3*	*p-value*
Peak VO2 - ml/kg/min	-0.164 [-0.250;-0.078]	**<0.001**	-0.098 [-0.183;-0.014]	**0.023**	-0.118 [-0.219;-0.018]	**0.021**
Six-Minute Walk Distance - m	-5.92 [-8.05;-3.80]	**<0.001**	-3.95 [-6.05;-1.85]	**<0.001**	-3.87 [-6.31;-1.43]	**0.002**
SF-36 Physical Functioning scale	-1.40 [-1.95;-0.838]	**<0.001**	-1.29 [-1.86;-0.719]	**<0.001**	-1.17 [-1.86;-0.482]	**0.001**
NYHA Class	+0.016 [0.007;0.025]	**<0.001**	+0.012 [0.003;0.021]	**0.009**	+0.014 [0.004;0.024]	**0.007**
LV Ejection Fraction - %	+0.147 [-0.049;0.343]	0.142	+0.079 [-0.124;0.282]	0.445	+0.139 [-0.107;0.386]	0.268
E/e' (medial) velocity ratio	+0.130 [0.029;0.232]	**0.012**	+0.067 [-0.036;0.171]	0.203	+0.027 [-0.091;0.145]	0.653
LA Volume Index - ml/m²	+0.313 [0.102;0.524]	**0.004**	+0.232 [0.019;0.444]	**0.033**	+0.148 [-0.078;0.375]	0.199
LV Mass Index – g/m²	-0.465 [-1.17;0.244]	0.198	-0.539 [-1.24;0.164]	0.133	-0.543 [-1.39;0.306]	0.209

Model 1: Galectin-3 only. **Model 2:** Galectin-3 adjusted by sex and age. **Model 3:** Galectin-3 adjusted by sex, age, atrial fibrillation, blood pressure (mean arterial pressure), eGFR [mL/min/1.73m²], and hemoglobin [g/dl].

Fig. 1:
The course of Galectin-3 levels during 12 months of follow up

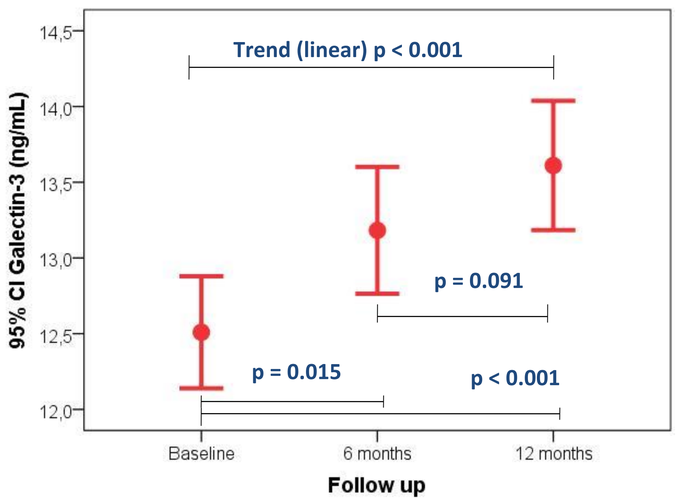

Fig. 3: Galectin-3 levels at baseline and hospitalization/ mortality rates during follow up

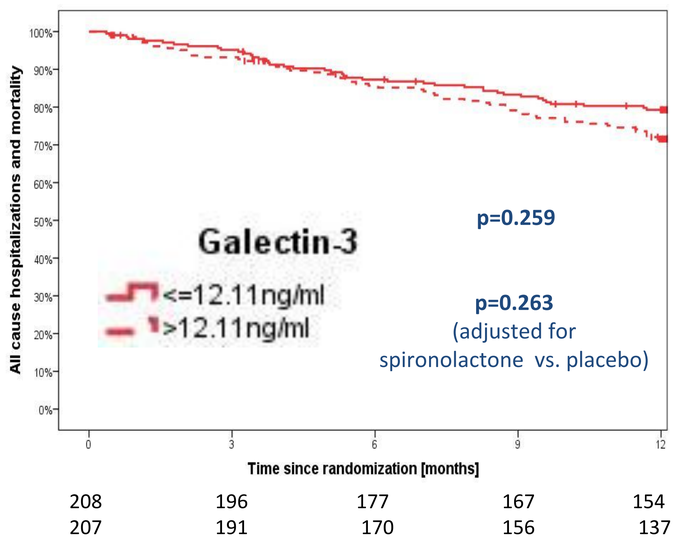

Fig. 2:
The course of Galectin-3 levels within both study arms

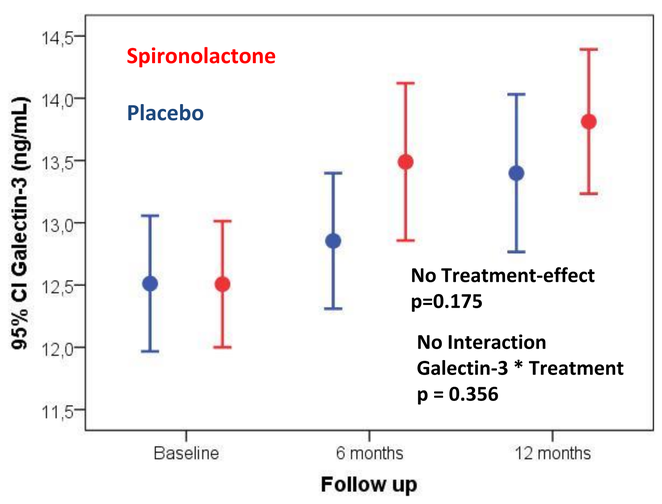

Fig. 4: Time dependent course of Galectin-3-levels and hospitalization/mortality rates during follow up.

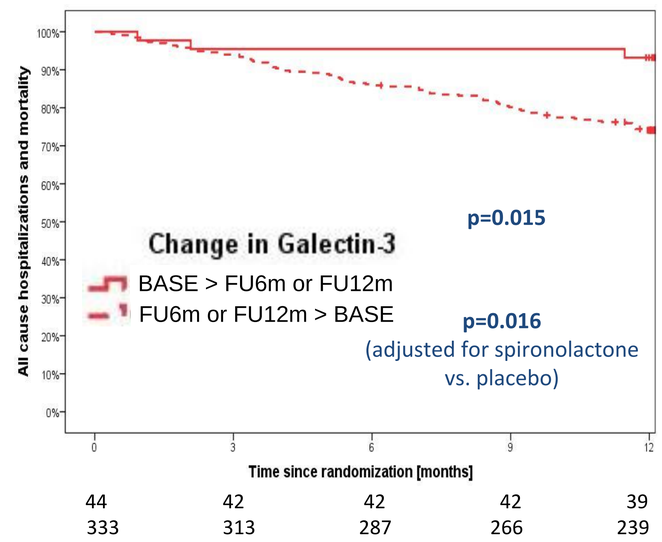

Table 3: The increase of Galectin-3 predicts worse prognosis – independent of spironolactone treatment or NT-proBNP levels.

	Model 1	*p-value*	*Model 2*	*p-value*	*Model 3*	*p-value*
Gal-3 at Median [12.11ng/ml]	1.242 [0.852;1.811]	0.259	1.197 [0.812;1.767]	0.364	1.170 [0.773;1.772]	0.457
Gal-3 at Median [12.11ng/ml] by arm*	1.240 [0.851;1.808]	0.263	1.196 [0.811;1.764]	0.367	1.170 [0.773;1.772]	0.457
Gal-3 at Median [12.11ng/ml] by NT-proBNP**	1.126 [0.755;1.680]	0.561	1.111 [0.740;1.669]	0.611	1.104 [0.721;1.689]	0.650
Gal-3 increased (FU6 or FU12m)	3.475 [1.277;9.451]	**0.015**	3.480 [1.277;9.484]	**0.015**	3.319 [1.214;9.073]	**0.019**
Gal-3 increased (FU6 or FU12m) by arm*	3.445 [1.265;9.388]	**0.016**	3.453 [1.265;9.427]	**0.016**	3.319 [1.214;9.073]	**0.019**
Gal-3 increased (FU6 or FU12m) by NT-proBNP**	3.304 [1.214;8.996]	**0.019**	3.291 [1.206;8.975]	**0.020**	3.127 [1.144;8.549]	**0.026**

Values are HR (95%-CI) by Cox regression. HR (Hazard Ratio) denotes time dependent risk
Model 1: biomarker group.
Model 2: biomarker group adjusted by sex and age.
Model 3: biomarker group adjusted by sex, age, atrial fibrillation, blood pressure (mean arterial pressure), eGFR [mL/min/1.73m²] and hemoglobin [g/dl]
*every Model additionally adjusted by treatment group, **every Model additionally adjusted by log_2-NTproBNP

Conclusion

Higher Galectin-3 levels are associated with impaired functional capacity in HFPEF. Galectin-3 levels increased over 12 months, and spironolactone did not modify this increase. The increase of Galectin-3 was, also after multiple adjustments including NT-proBNP and treatment arm, highly predictive for an increased rate of hospitalizations or death.

Contact: Dr. Kathleen Durstewitz, email: kathleen.durstewitz@med.uni-goettingen.de

Disclosures: nothing to disclose