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ORIGINAL PAPER

Prognostic value of galectin-3, a novel marker of fibrosis, in patients with chronic heart failure: data from the DEAL-HF study

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Abstract
Aims Biomarkers are increasingly being used in the management of patients with chronic heart failure (HF). Galectin-3 is a recently developed biomarker associated with fibrosis and inflammation, and it may play a role in cardiac remodeling in HF. We determined its prognostic value in patients with chronic HF.
Methods and results Patients with chronic HF (New York Heart Association functional class III or IV) who participated in the Deventer–Alkmaar heart failure study were studied. Galectin-3 levels were determined at baseline using a novel optimized enzyme-linked immunosorbent assay. Univariate and multivariate analyses were used to determine the prognostic value of this biomarker. We studied 232 patients; their mean age was 71 ± 10 years, 72% were male, and 96% were in NYHA class III. During a follow-up period of 6.5 years, 98 patients died. Galectin-3 was a significant predictor of mortality risk after adjustment for age and sex, and severity of HF and renal dysfunction, as assessed by NT-proBNP and estimated glomerular filtration rate, respectively (hazard ratio per standard deviation 1.24, 95% CI 1.03–1.50, $P = 0.026$).
Conclusion Plasma galectin-3 is a novel prognostic marker in patients with chronic HF. Its prognostic value is independent of severity of HF, as assessed by NT-proBNP levels, and it may potentially be used in the management of such patients.

Keywords Galectin-3 · Chronic heart failure · Biomarkers · Prognosis

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Introduction

Heart failure (HF) is a large medical and epidemiological problem, and recent studies, both in *acute* and *chronic* HF, indicate that it is still associated with a high morbidity and mortality [1–3]. Early identification of high-risk patients may favorably affect outcome and biomarkers are increasingly being recognized to have important clinical value in this respect [3]. After the initial insult to the myocardium, HF is a disease with autonomic progression associated with ventricular dysfunction and cardiac remodeling [4]. Natriuretic peptides, in particular brain natriuretic peptide (BNP) and its N-terminal part NT-proBNP, are increasingly being used to guide the management of HF patients [3]. Although this concept has proven to be successful, BNP and NT-proBNP values are very much influenced by many factors including age, renal function, and anemia [5]. As a result, the search for new biomarkers, which might reflect other disease processes, and which might be of additional and independent value has continued. Indeed, with the acknowledgement of remodeling as a determinant of disease progression and poor prognosis, it has become imperative to identify those patients with the highest risk of adverse outcome, thus enabling a more personalized management of HF.

Galectin-3 is a soluble β-galactoside-binding lectin [6] that plays an important regulatory role in cardiac fibrosis and remodeling, which are key contributing mechanisms to

the development and progression of HF [4]. Galectin-3 was found to be increased in patients with acutely decompensated and unstable HF [7, 8]. The involvement of galectin-3 in the development of fibrosis has been demonstrated not only in the liver [9] and in the kidney [10], but in the heart as well [11, 12]. Taken together, these observations suggest that measuring galectin-3 levels may potentially be useful in a wider range of HF patients [13] to determine their risk in general and to examine the value of this new biomarker when added to conventional risk markers. Accordingly, we studied the clinical value of galectin-3 in a population of patients with stable advanced HF, who had been very well clinically characterized, and who were enrolled in the Deventer–Alkmaar heart failure study (DEAL-HF) [14].

Methods

Study design and patient population

The original DEAL-HF study was a prospective, randomized, parallel group, controlled study conducted at two regional teaching hospitals in The Netherlands. The study design and methods have been described in detail previously [14]. Briefly, 240 patients with the NYHA functional class III or IV HF were randomized between 2000 and 2003 to a disease management program or not. The primary endpoints were all-cause mortality and hospitalization for HF and the duration of the study was 12 months. In the present study, the follow-up was extended, and only vital status (and not intermittent hospitalizations) were assessed during long-term follow-up, for obvious reasons [15]. The official day of assessment was September 15, 2006. The protocol was approved by the local Medical Ethics Committees and the study complied with the *Declaration of Helsinski*. Written informed consent was given by all patients.

Galectin-3 measurements

At baseline, 10 mL of blood was drawn from the antecubital vein of all patients and transferred in chilled disposable tubes containing aprotinin. The blood samples were then centrifuged at 3,500 rpm for 15 min at 4°C, the plasma was transferred into 1 mL cryotubes, and stored at −70°C for later analyses.

Plasma galectin-3 levels were determined using a novel and optimized enzyme-linked immunosorbent assay kit (Galectin-3 Assay™, BG Medicine, Waltham, MA, USA) and were measured on a Bio-tekELx800 microplate reader (Biotek Instruments, Winooski, VT, USA). Calibration of the assay was performed according to the manufacturer's recommendations and values were normalized to a standard curve.

Of the 240 patient baseline plasma samples, eight samples had insufficient sample volume remaining to perform the galectin-3 measurement. As such, there are a total of 232 baseline galectin-3 measurement results.

Other biochemical measurements

NT-proBNP levels were determined by an immunoelectrochemiluminesence method (Elecsys, Roche Diagnostics, Basel, Switzerland) [5].

The estimated glomerular filtration rate (eGFR) as an indicator of renal function, was estimated from serum creatinine using a formula that accounts for the influence of age on creatinine production, which has been validated in patients with HF, and was described in detail elsewhere (MDRD) [16].

Statistical analyses

Galectin-3 values were categorized into quartiles based upon their distribution among all patients and a Kaplan–Meier product limit analysis was performed. The log-rank test was used to test equality of estimated survival distribution functions across quartiles of galectin-3. In addition, the association between galectin-3 level and the instantaneous relative risk of death from any cause was analyzed using a Cox proportional hazards regression analysis and Kaplan–Meier product limit estimation. A univariate Cox proportional hazards regression model with galectin-3 as the predictor variable was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) associated with baseline galectin-3 value and death from any cause. Galectin-3 value was examined continuously [expressed per standard deviation (SD)] and categorized as a binary predictor variable based on a previously determined cut-off value of 17.7 ng/mL, which represents the recommended upper limit of normal value for galectin-3 (Personal communication, BG Medicine Inc., Waltham, MA, USA, February 2009). Evaluation of the assumption of proportional hazards was positively evaluated by inspection of log (-survival) values as a function of survival time across galectin-3 categories. The Wald chi-square P value was used to evaluate the statistical significance of the Cox regression model. Multivariable Cox regression models were also evaluated to assess the effect of galectin-3 on mortality after adjusting for NT-proBNP, age, gender, and creatinine clearance rate. In one patient NT-proBNP measurement was not available, therefore all multivariable models including NT-proBNP were conducted based upon 231 patients. Results for baseline characteristics are presented as mean ± SD. Receiver operating characteristic

(ROC) curve analysis was performed. We considered sensitivity and specificity of equal importance, in ROC analyses, the best prognosticators for survival status were considered to be those parameters that gave the highest product of sensitivity and specificity for predicting death. Spearman correlation coefficients were calculated to determine which clinical and biochemical variable had a univariate correlation with Galectin-3. Statistical analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC, USA).

Results

A total of 232 baseline plasma samples from HF patients, enrolled in the DEAL-HF study, were available and included in the analysis. Baseline characteristics grouped according to the galectin-3 levels are depicted in Table 1. Overall, mean age was 71 ± 10 years, 72% were male and 96% were in the NYHA functional class III. Co-morbidities included diabetes mellitus in 30% and chronic obstructive pulmonary disease in 29%. The mean creatinine clearance rate was 55.0 ± 22.8 mL/min and the median NT-proBNP level was 253 pmol/L (2,140 pg/mL). The mean follow-up time of the surviving patients was 4.0 ± 1.9 years.

Galectin-3 values

One hundred and fourteen patients (49%) had galectin-3 plasma levels above the upper limit of normal cut-off value of 17.7 ng/mL. For all study subjects, the mean levels of galectin-3 across quartiles were 18.6 ± 7.8 ng/mL (Table 1). Galectin-3 levels were associated with age ($r = 0.318$, $P < 0.001$), and younger patients had lower levels. Galectin-3 was also associated with renal dysfunction (GFR) ($r = -0.619$, $P < 0.001$) and higher levels were found in patients with more renal dysfunction. Galectin-3 levels were also increased in patients with higher NT-proBNP levels ($r = 0.265$, $P < 0.001$). Finally, a borderline, statistically significant association was found with body mass index (BMI) ($r = -0.154$, $P = 0.022$). There was neither a significant correlation between galectin-3 levels and left ventricular ejection fraction nor etiology of HF.

Galectin-3 levels and mortality

Overall, 98 patients died during the follow-up period. Patients who died were older ($P = 0.03$) and more often male ($P = 0.04$). In addition, both NT-proBNP levels (577 ± 751 vs. 363 ± 477 pmol/L, $P = 0.01$) and galectin-3 levels (20.1 ± 8.1 vs. 17.5 ± 7.4 ng/mL, $P = 0.01$)

Table 1 Baseline demographic and clinical characteristics of the study population by quartile of galectin-3 levels

Baseline characteristic	All subjects $n = 232$	Galectin-3 quartile				*P* value
		1 (<13.63 ng/mL) $n = 58$	2 (13.63–17.63 ng/mL) $n = 59$	3 (17.64–21.62 ng/mL) $n = 57$	4 (>21.62 ng/mL) $n = 58$	
Age, mean (SD) (years)	70.9 (10.0)	64.6 (11.7)	71.6 (8.9)	72.8 (8.9)	74.6 (7.0)	<0.001
Male (%)	72.4	72.4	76.3	68.4	72.4	N/S
Ischemic etiology (%)	62.5	50.0	70.2	61.0	69.0	0.047
NYHA functional class (%)						
III	96	97	100	93	93	N/S
IV	4	2	0	6	7	N/S
LVEF, mean (SD)	30.9 (9.4)	31.1 (10.0)	29.7 (8.2)	31.9 (8.7)	31.0 (10.6)	N/S
BMI, mean (SD) (kg/m^2)	26.3 (4.7)	27.9 (5.3)	25.9 (4.1)	25.8 (4.7)	25.9 (4.3)	0.046
Diabetes mellitus (%)	30	28	22	35	33	N/S
COPD (%)	29	25	23	32	35	N/S
Smoker (%)	13	17	12	14	9	N/S
GFR, mean (SD) (mL/min)	55.0 (22.8)	72.7 (24.5)	56.0 (18.6)	49.2 (19.4)	42.3 (16.6)	<0.001
NT-proBNP level, mean (SD) (pmol/L)	456.0 (616.7)	291.1 (376.6)	353.8 (386.7)	526.5 (561.1)	651.2 (920.4)	0.005
Galectin-3 level, mean (SD) (ng/mL)	18.6 (7.8)	11.3 (1.6)	15.5 (1.3)	19.5 (1.2)	28.2 (9.0)	–

Percentages may not sum to 100 due to rounding. *P* values are from one-way ANOVA comparison of means across quartiles of galectin-3

BMI Body mass index, *COPD* chronic obstructive pulmonary disease, *LVEF* left ventricular ejection fraction, *NYHA* New York Heart Association, *SD* standard deviation, *N/S* not significant

were significantly higher in patients who died, than in survivors.

ROC curve analysis revealed an area under the curve (AUC) of 0.612 [0.538–0.685], $P = 0.004$ for Galectin-3. Similar results yielded for NT-proBNP: AUC of 0.611 [0.538–0.685], $P = 0.004$. We found that the highest product of sensitivity and specificity was seen with gal-3 levels of 17.72 ng/mL.

Figure 1 shows the Kaplan–Meier survival curves according to quartiles of galectin-3. There was a gradual increase in all-cause mortality across the galectin-3 quartiles (log-rank $P = 0.048$).

Adjustment for patient baseline age, gender, baseline eGFR and baseline NT-proBNP value minimally attenuated the association of baseline galectin-3 level with outcome, with galectin-3 remaining a significant predictor. The effects of these covariates appear in Table 2. In the fullest model that incorporates NT-proBNP, age, gender and creatinine clearance rate, the HR associated with galectin-3 per SD was HR 1.24 (95% CI 1.03–1.50, $P = 0.026$).

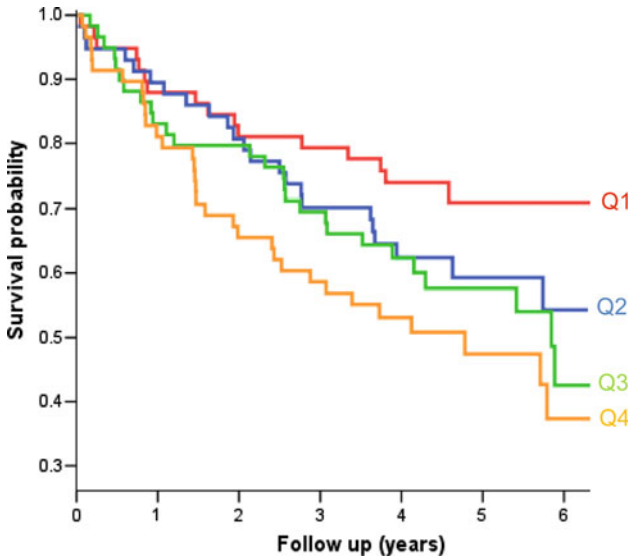

Fig. 1 Kaplan–Meier curves according to quartiles of baseline galectin-3 values. Log-rank $P = 0.048$. *Q1* galectin-3 values <13.63 ng/mL, *Q2* 13.63–17.63 ng/mL, *Q3* 17.64–21.62 ng/mL, *Q4* >21.62 ng/mL

The incremental risk of the combination of galectin-3, dichotomized into below and above normal values with NT-proBNP, dichotomized above and below the median, was also considered. Figure 2 presents the mortality within four categories of the combination of galectin-3 and NT-proBNP. Patients with high baseline levels of both galectin-3 and NT-proBNP were observed to have an approximately 1.5- to 2-fold higher mortality rate compared to patients in other categories ($P = 0.036$ for trend).

Discussion

The main finding of the present study is that galactin-3 is an independent predictor of mortality in this population of patients with moderate to advanced chronic HF. Although increased levels of galectin-3 were associated with increasing age, progressive renal dysfunction and severity

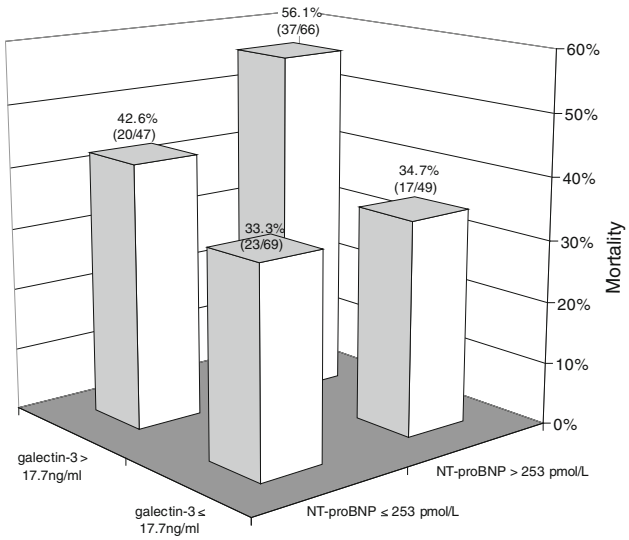

Fig. 2 Mortality as a function of baseline galectin-3 and NT-proBNP categories. The median value of NT-proBNP (253 pmol/L), was used to define two levels of NT-proBNP concentration. Of the 232 subjects, 231 had both a galectin-3 and NT-proBNP measurement. The number of patients in the each category is as follows: high galectin-3 and high NT-proBNP ($n = 66$); low galectin-3 and low NT-proBNP ($n = 69$); low galectin-3 and high NT-proBNP ($n = 49$); high galectin-3 and low NT-proBNP ($n = 47$)

Table 2 Univariate and adjusted multivariable hazard ratios for galectin-3 association with mortality

	HR (95% CI) for galectin-3	*P* value
Univariate (galectin-3 only) per standard deviation (7.8 ng/mL)	1.24 (1.08–1.43)	0.003
+NT-proBNP	1.28 (1.07–1.52)	0.006
+NT-proBNP + age + gender	1.25 (1.05–1.49)	0.014
+NT-proBNP + age + gender + GFR	1.24 (1.03–1.50)	0.026

The stated *P* value is associated with the regression coefficient of galectin-3 in each model

of HF as assessed by increasing levels of NT-pro BNP, galectin-3 remained an independent prognostic marker.

The present data extend earlier findings in patients with acutely decompensated HF [8] and in those with terminal, end-stage HF who required mechanical circulatory support [9]. In the study by van Kimmenade et al. [8], galactin-3 was measured in 599 patients with acute dyspnea who presented to the emergency department, of whom 209 were diagnosed as "acute HF". Galectin-3 levels were higher in those with acute HF than in those who did not (9.2 vs. 6.9 ng/mL; $P < 0.001$), and the ROC curve of galactin-3 for the diagnosis of HF was 0.72 ($P < 0.001$) as compared to a ROC curve for NT-pro BNP of 0.94 ($P < 0.001$; difference with galectin-3 $P < 0.001$). For predicting 60-day mortality, ROC curves were higher for galectin-3 (0.74, $P < 0.001$) than for NT-pro BNP (0.67, $P = 0.009$; difference with galectin-3, $P = 0.05$). In the study by Milting et al. [9], 55 patients with end-stage HF were compared to 40 healthy controls, and galectin-3 levels were higher in HF patients than in controls (11 vs. 4.1 ng/mL, $P < 0.05$), but galectin-3 did not decrease after ventricular assist device support (in contrast to BNP levels). However, patients who died or in whom multi-organ failure developed, had significantly higher galectin-3 levels compared to those who successfully bridged to transplantation. In the present study, galectin-3 levels were elevated in only half of our population of patients with advanced but stable HF. As a biomarker to detect (or exclude) HF, this percentage is rather low, as compared to for example BNP in which around 90% of similar patients were found to abnormal levels [17]. In contrast to its diagnostic properties, the prognostic value of galectin-3 appears to be high. Both in the two earlier studies in acute unstable HF, as well as in the present study in relatively stable HF patients, galectin-3 was an independent predictor of outcome during follow-up and as such, it appears to be a promising new biomarker in HF [18].

Galectin-3 promotes macrophage migration, fibroblast proliferation and collagen synthesis, or the development of fibrosis [14]. In a recent study, the independent association between excessive extracellular matrix turnover and poor outcome in patients with HF was reported and this was particularly true for the serum collagen marker PIIINP (N-terminal type III collagen peptide) [19]. Recent work from Taiwan [20] has shown that Galectin-3 is significantly correlated with this PIIINP, but also with other (serum) markers of extracellular matrix turnover, such as matrix metalloproteinase-2 (MMP-2) and tissue inhibitor of metalloproteinase-1 (TIMP-1).

Galectin-3 levels were significantly associated with the severity of renal dysfunction in this study, but retained prognostic value after correction for eGFR. This finding is interesting since increased galectin-3 is also associated with renal fibrosis [10], and the same process may thus affect both heart and kidneys. Renal dysfunction is one of the most powerful predictors of prognosis in HF and plays an important role in its pathophysiology [21] and the "overlap" may thus also be mediated by galectin-3.

After an initial insult to the myocardium, cardiac remodeling occurs as a compensatory mechanism, and this will ultimately lead to left ventricular dysfunction and HF. This complex process with an increase of left ventricular wall thickness and dilatation and reshaping of the left ventricle leads to lengthening or hypertrophy of cardiomyocytes with insufficient angiogenesis leading to metabolic and ischemic problems [22]. Activation and proliferation of fibroblasts, which increases the synthesis of fibrillar collagen and activates the inflammatory response, plays an important role in this process [23–25]. Galectin-3 is likely to play a role in this process, and has been shown to interact with various ligands located at the extracellular matrix [26]. In a very recent study from the US, intrapericardial infusion of galectin-3 for 4 weeks in adult male rats led to (1) enhanced macrophage and mast cell infiltration, increased cardiac interstitial and perivascular fibrosis, and cardiac hypertrophy, (2) increased TGF-β expression, and (3) decreased cardiac performance, as for example shown by systolic and diastolic cardiac performance [27]. Given these findings, it would be tempting to speculate that blockade or inhibition of galectin-3 could have favorably affect this process and be a target for treatment, but to our knowledge, such data are not (yet) available.

The main limitation of the current study is its relatively small size. Furthermore, we measured galectin-3 on a single time point and thus can only speculate on its importance over time. Because of these limitations, we regard our study mainly as a hypothesis-generating study. Nevertheless, galectin-3 is a novel biomarker in patients with HF, which seems to have important prognostic value. Although it is generally elevated in HF, this prognostic value is independent of the severity of disease, as assessed by NT-proBNP levels.

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