Galectin-3: A new biomarker for the diagnosis, analysis and prognosis of acute and chronic heart failure

Galectin-3 : un nouveau biomarqueur pour le diagnostic, l’analyse et le pronostic de l’insuffisance cardiaque aiguë et chronique

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Received 21 January 2013; received in revised form 23 June 2013; accepted 24 June 2013
Available online 3 October 2013

KEYWORDS
Galectin-3; Heart failure; Diagnosis; Prognosis; Mortality

Summary  Heart failure constitutes an important medical, social and economic problem. The prevalence of heart failure is estimated as 2–3% of the adult population and increases with age, despite the scientific progress of the past decade, especially the emergence of natriuretic peptides, which have been widely used as reliable markers for diagnostic and prognostic evaluation. Identification of new reliable markers for diagnosis, analysis, prognosis of mortality and prevention of hospitalization is still necessary. Galectin-3 is a soluble β-galactoside-binding protein secreted by activated macrophages. Its main action is to bind to and activate the fibroblasts that form collagen and scar tissue, leading to progressive cardiac fibrosis. Numerous experimental studies have shown the important role of galectin-3 in cardiac remodelling due to fibrosis, independent of the fibrosis aetiology. Galectin-3 is significantly increased in chronic heart failure (acute or non-acute onset), independent of aetiology. Some clinical studies have confirmed the predictive value of galectin-3 in all-cause mortality in patients with heart failure. In our

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Abbreviations: Ac-SDKP, N-Acetyl-Seryl-Aspartyl-Lysyl-Proline; BNP, B-type Natriuretic Peptide; CI, Confidence Interval; EDTA, Ethylenediaminetetra-acetic Acid; GFR, Glomerular Filtration Date; HF, Heart Failure; HR, Hazard Ratio; LVEF, Left Ventricular Ejection Fraction; MMP-2, Log Matrix Metalloproteinase-2; NT-proBNP, N-terminal Prohormone of B-type Natriuretic Peptide; NYHA, New York Heart Association; OR, Odds Ratio; PIILNP, N-terminal Propeptide of Type III Procollagen; TIMP1, Log Tissue Inhibitor of Metalloproteinase-1.

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http://dx.doi.org/10.1016/j.acvd.2013.06.054
Structural, biochemical and functional characteristics of galectin-3

Galectins, an ancient lectin family, are characterized by specific binding of β-galactosides through evolutionary conserved sequence elements of the carbohydrate-recognition domain. A structurally unique member of the family is galectin-3; in addition to the carbohydrate-recognition domain, it contains a proline- and glycine-rich N-terminal domain through which it is able to form oligomers. From the available data, galectin-3 is expressed in various tissues and cell types, and is detectable inside and outside cells as well as on cell surfaces. The biological roles of galectin-3 were initially attributed to its carbohydrate-binding activity, but during the past decade, a whole new spectrum of functions, unrelated to lectin activity, has been revealed [1].

Galectin-3 has been found to be involved in many biological processes, such as cell-cell and cell-extracellular matrix adhesion, cell growth and differentiation, the cell cycle, signalling, apoptosis and angiogenesis. Consequently, galectin-3 is involved in the regulation of development, immune reactions, tumourigenesis, tumour growth and metastasis [1,2].

Physiopathology

Cardiac remodelling is one of the main components of chronic heart failure (HF) [3]. Adaptation of cardiomyocytes is critical in the remodelling process. In response to acute and chronic damage, the immune cells recruit to the myocardium, with the production of cell-signalling proteins and the activation of fibroblasts and myofibroblasts, which lead to the deposition of procollagen into the extracellular matrix and cardiac fibrosis [4]. This part of the pathophysiological pathway is difficult to analyse using biomarkers and even by magnetic resonance imaging.

The up-regulation of myocardial galectin-3 has been demonstrated in a rat model of HF-prone hypertensive hearts [5], interferon 6-induced murine chronic active myocarditis and cardiomyopathy, rat streptozocin-induced diabetic cardiomyopathy and rat angiotensin II-induced hypertension; in several studies, this up-regulation was associated with the concomitant activation of macrophages. Galectin-3 has also been found to be significantly up-regulated in the hypertrophied hearts of patients with aortic stenosis and in the plasma of patients with acute and chronic HF. Galectin-3 may be involved in the development of HF. It is speculated that blockade of galectin-3 may slow the progression of HF and possibly reduce HF-related morbidity and mortality. On the other hand, there are strong arguments that connect cardiac remodelling with galectin-3 biology, such as decreased negative change in the pressure over time response to isoproterenol challenge, the ratio of early left ventricular filling phase to atrial contraction phase and left ventricular ejection fraction (LVEF) [6].

Experimental studies

Sharma et al. [5] showed that galectin-3 infusion into the pericardium of normal rats led to the development of cardiac remodelling. The highest expression level of galectin-3 protein was observed in the same group of animals that had the highest degree of cardiac fibrosis and had developed HF by 12–14 weeks (densitometric units: HF 94.66–9.5; compensated 35–5.6; controls, 27.2–6.2; P < 0.05 versus compensated and controls). A computer-assisted densitometric analysis of the picrosirius red-stained sections for the quantification of myocardial collagen revealed a higher degree of interstitial collagen content in the failing Ren-2 rats compared with compensated and wild-type rats (interstitial collagen volume fraction percentage: HF 7.8–0.38; compensated 3.8–0.54; wild-type 2.5–0.3; P < 0.05 versus compensated and wild-type). Liu et al. [6] also confirmed the pathogenic effects of intrapericardial
infusion of galectin-3 in adult male rats. Macrophages (ED1-positive cells) in the myocardium increased significantly in the galectin-3 treatment group compared with vehicle (P < 0.01). There was also a significant increase in mast cell density in the galectin-3 treatment group compared with vehicle (P < 0.01).

An experimental study by de Boer et al. [7] showed that an early increase in galectin-3 expression identified failure-prone hypertrophied hearts. Galectin-3, a macrophage-derived mediator, induces cardiac fibroblast proliferation, collagen deposition and ventricular dysfunction. This implies that HF therapy aimed at inflammatory responses may need to be targeted at the early stages of HF and probably needs to antagonize multiple inflammatory mediators, including galectin-3. In the same way, in myocardial biopsies of aortic stenosis patients undergoing aortic valve replacement [5], myocardial galectin-3 expression was increased in patients with a depressed ejection fraction compared with in those with a compensated form of cardiac hypertrophy (7.08 ± 1.17 vs 4.60 ± 0.51; P < 0.05).

Measuring range and variability

The galectin-3 measuring range is 1.4–94.8 ng/mL for clinical specimens [8]. Galectin-3 results were equivalent when measured in serum or ethylenediaminetetra-acetic acid (EDTA) plasma. The 90th, 95th and 97.5th percentiles of the normal reference interval were 17.6, 20.3 and 22.1 ng/mL, respectively. Imprecision studies demonstrated that the total coefficient of variation was <10% at a low concentration of 6 ng/mL, 7% near the mid-level concentration of 21 ng/mL and 15% at the high concentration of 70 ng/mL. The limit of blank was 0.86 ng/mL, the limit of detection was 1.13 ng/mL and the limit of quantification was 0.96 ng/mL. The linear measurement range was 0.96–130 ng/mL and there was no high-dose hook at concentrations up to 500 ng/mL. Samples can be stored for up to 15 days at either 22–28 °C or 2–8 °C before analysis; measurements are stable after storage at −20 °C or −70 °C for at least 6 months and through six freeze-thaw cycles. No cross-reactivity with nine compounds structurally related to galectin-3 and no interference from 22 common medications, icterus or lipaemia were found. Haemolysis is known to interfere with the measurement of galectin-3. The presence of human anti-mouse antibodies or rheumatoid factor may interfere with the galectin-3 assay, which could cause falsely elevated results. Galectin-3 results should be interpreted with caution in patients with a history of therapeutic use of murine monoclonal antibodies (immunoglobulin G) or their fragments, or who have known autoimmune disorders. Specimens with high concentrations of gamma globulin (≥2.5 g/dL) may have false elevation of results. Galectin-3 results from patients with diseases associated with hyperglobulinaemia, such as multiple myeloma, should be interpreted with caution.

A laboratory sample analysis of 1092 healthy volunteers aged ≥ 55 years from the Biolmage cardiovascular risk study showed that the central 95% normal reference interval of galectin-3 measured by the galectin-3 assay was 3.8–21.0 ng/mL; galectin-3 was detectable in the plasma of all healthy individuals and exhibited a normal distribution [8].

Associated factors

These factors are usually markers associated with myocardial fibrosis. Indeed, in the PREVEND study, galectin-3 concentrations were measured in 7968 individuals from the general population [9]. Galectin-3 concentrations were slightly higher in women and increased from age 30 years to 75 years by approximately 1.5 ng/mL. Significant positive associations were found with age, sex, diabetes, hypertension, hypercholesterolaemia, body mass index, renal function (P < 0.001 for all) and smoking (P < 0.002) [10]. However, this relationship was not confirmed by Shah et al. [11] in a decompensated HF cohort (did not differ according to sex [P = 0.92], ethnicity [P = 0.48], diabetic status [P = 0.58] or ischaemic cause [P = 0.24]). There is <0.5% cross-reactivity with other galectin isoforms (galectin 1, 2, 4, 7, 8, 9 and 12) and collagen (I and III). The galectin-3 assay can be used to measure galectin-3 concentrations in both serum and EDTA plasma samples. In the DEAL-HF study [12], galectin-3 concentrations were associated with age (r = 0.318; P = 0.001); younger patients had lower concentrations. Galectin-3 was also associated with renal dysfunction (glomerular filtration rate [GFR]) (r = −0.619; P = 0.001); higher concentrations were found in patients with severe renal dysfunction (GFR < 30 mL/min). Finally, a borderline statistically significant association was found with body mass index (r = −0.154; P = 0.022).

Clinical studies

Screening assessment

The PREVEND study [9] showed that the highest quintile of galectin-3 (median 15.6 ng/mL) had a 15% 10-year mortality rate compared with a 5% rate for those in the lowest quintile (median 7.7 ng/mL).

Galectin-3 concentrations were measured in 3353 participants in the Framingham Offspring Cohort [10] (mean age 59 years; 53% women). The relationship between galectin-3 and incident HF was assessed using proportional hazards regression. Galectin-3 was associated with increased left ventricular mass in age- and sex-adjusted analyses (P = 0.001); this association was attenuated in multivariable analyses (P = 0.06). A total of 166 participants developed incident HF and 468 died during a mean follow-up period of 11.2 years. Galectin-3 was associated with risk of incident HF (hazard ratio [HR] 1.28 per 1 SD increase in log galectin-3, 95% confidence interval [CI] 1.14–1.43; P = 0.0001) and remained significant after adjustment for clinical variables and B-type natriuretic peptide (BNP) (HR 1.23, 95% CI 1.04–1.47; P = 0.02). Galectin-3 was also associated with risk of all-cause mortality (multivariable-adjusted HR 1.15, 95% CI 1.04–1.28; P = 0.01). The addition of galectin-3 to clinical factors resulted in negligible changes to the C-statistic and minor improvements in the net reclassification index.
In the PROVE IT-TIMI 22 study [13], 100 patients who developed HF after acute coronary syndrome had a higher baseline galectin-3 concentration (median 16.7 ng/L [25th, 75th percentile 14.0, 20.6] vs 14.6 ng/L [12.0, 17.6]; P = 0.004).

Patients with a baseline galectin-3 concentration above the median had an odds ratio (OR) of 2.1 (95% CI 1.2–3.6) for developing HF (P = 0.010). Galectin-3 showed a graded relationship with risk of HF. Cases were more likely to have hypertension, diabetes, prior myocardial infarction and prior HF; after adjustment for these factors, this graded relationship with galectin-3 quartile and HF remained significant (adjusted OR 1.4, 95% CI 1.1–1.9; P = 0.020).

**Acute heart failure assessment**

Due to its physiopathology, there is no clear proof of the effectiveness of galectin-3 for the diagnosis of HF; in most cases, natriuretic peptides and echocardiography demonstrated high accuracy.

However, the prognostic power of galectin-3 has undergone more assessment. The PRIDE study for assessment of acute HF was a multicentre study that enrolled 599 consecutive patients with acute or decompensated HF and proved the key value of measuring N-terminal prohormone of BNP (NT-proBNP) to help clinicians to diagnose HF [14]. The PRIDE study population was drawn from consenting patients aged >21 years who presented to the emergency department. Exclusion criteria for the study were severe renal insufficiency (serum creatinine concentration >2.5 mg/dL), dyspnoea after chest trauma, dyspnoea secondary to severe coronary ischaemia that was identified as >0.1 mV ST-segment elevation or ST-segment depression on a 12-lead electrocardiogram if performed at presentation, >2-hour delay after urgent intravenous loop diuretic administration (above any baseline maintenance dose) and unblinded measurement of natriuretic peptide concentration. Patients who developed HF had a higher baseline galectin-3 concentration (median 16.7 µg/L [25th, 75th percentile 14.0, 20.6] vs 14.6 µg/L [12.0, 17.6]; P = 0.004).

Patients with a baseline galectin-3 concentration above the median had an OR of 2.1 (95% CI 1.2–3.6) for developing HF (P = 0.010). Galectin-3 showed a graded relationship with risk of HF. Cases were more likely to have hypertension, diabetes, prior myocardial infarction and prior HF; after adjustment for these factors, this graded relationship with galectin-3 quartile and HF remained significant (adjusted OR 1.4, 95% CI 1.1–1.9; P = 0.020). Galectin-3 medians and interquartile ranges were 9.2 (7.4–12.1) in HF patients and 6.9 (5.2–8.7) in non-HF patients. Compared with NT-proBNP and all clinical data available in those studies, the elevated concentration of galectin-3 was best independent predictor of 60-day mortality (OR 10.3; P < 0.01) and 60-day death/recurrent HF (OR 14.3; P < 0.001).

Shah et al. [11] evaluated 115 consecutive patients with acute dyspnoea and found that dyspnoeic patients with HF and galectin-3 concentrations higher than the median value of 15.0 (11.1–19.7) had a 63% 4-year mortality rate; by comparison, patients with concentrations lower than 11.0 (9.1–14.4) had a 37% mortality rate (P = 0.003).

### Chronic heart failure assessment

Galectin-3 concentration was measured by de Boer et al. [15] in 592 participants hospitalized with HF from the COACH disease management trial. Concentrations of galectin-3 were measured prior to discharge from the hospital and again at approximately 6-month follow-up. Although concentrations were stable over this period, the baseline concentration and a 100% increase in galectin-3 from baseline were independent predictors of HF rehospitalization and death after adjustment for age, sex and natriuretic peptide concentrations: adjusted HRs of 3.34 (95% CI 2.23–5.01; P < 0.001, baseline fourth quartile) and 1.77 (95% CI 1.42–2.20; P < 0.001 doubling from baseline), respectively. A doubling of galectin-3 concentration over 6 months was associated with an HR of 1.97 (1.62–2.42) for the primary outcome (P = 0.001). After correction for age, sex, BNP, estimated GFR and diabetes, the HR was 1.38 (1.07–1.78; P = 0.015). Galectin-3 concentrations were correlated with higher interleukin-6 and C-reactive protein concentrations (P = 0.002). The predictive value of galectin-3 was stronger in patients with preserved LVEF (n = 114) compared with patients with reduced LVEF (P = 0.001). Galectin-3 is an independent marker for outcome in HF and appears to be particularly useful in HF patients with preserved LVEF. Considering HF therapy, plasma galectin-3 concentrations at admission were lower in patients receiving beta-blockers (13.4 ng/mL, interquartile range 11.9–16.3 vs 14.9 ng/mL, interquartile range 12.6–17.6; P = 0.024) and spironolactone (13.1 ng/mL, interquartile range 11.0–15.3 vs 14.3 ng/mL, interquartile range 12.3–17.2; P = 0.043) comparing with in untreated patients. In an another advanced decompensated HF cohort [15], there was no relationship between galectin-3 and echocardiographic or haemodynamic indexes, but higher galectin-3 concentration was associated with poor renal function (estimated GFR, r = −0.24, P = 0.007; cystatin C, r = 0.38, P < 0.001) and predicted all-cause mortality (HR 1.86, 95% CI 1.36–2.54; P < 0.001).

In data from DEAL-HF [12], a randomized study that enrolled 232 patients with chronic HF, 114 patients (49%) had galectin-3 plasma concentrations above the upper limit of the normal cut-off value of 17.7 ng/mL. For all study subjects, the mean concentration of galectin-3 across quartiles was 18.6 ± 7.8 ng/mL. There was no significant correlation between galectin-3 concentration and LVEF or aetiology of HF. Globally, the galectin-3 concentration was associated with an increased risk of mortality (HR 1.24, 95% CI 1.03–1.50; P = 0.26).

The galectin-3 concentration in ambulatory patients with chronic HF and systolic dysfunction was evaluated in the HF-ACTION study [16]. Galectin-3 was assessed at baseline in a cohort of 895 subjects with stored plasma samples available. The association between galectin-3 and clinical outcomes was assessed using a series of Cox proportional hazards models. Higher galectin-3 concentrations were associated with other measures of HF severity, including higher New York Heart Association (NYHA) class, lower systolic blood pressure, higher creatinine, higher NT-proBNP and lower maximal oxygen consumption. In unadjusted analysis, there was a significant association between elevated galectin-3 concentrations and hospitalization-free survival (unadjusted...
HR 1.14 per 3 ng/mL increase in galectin-3; \( P = 0.0001 \)). In multivariable modelling, the prognostic impact of galectin-3 was significantly attenuated by the inclusion of other known predictors.

Galectin-3 is elevated in ambulatory HF patients and is associated with poor functional capacity and other known measures of HF severity. In univariate analysis, galectin-3 was significantly predictive of long-term outcomes, but this association did not persist after adjustment for other predictors.

Tang et al. [17], who evaluated chronic HF and advanced decompensated HF in 178 patients, found that higher galectin-3 concentration was associated with poor renal function (estimated GFR, \( r = -0.24, P < 0.007 \); cystatin C, \( r = 0.38, P < 0.0001 \)) and predicted all-cause mortality (HR 1.86, 95% CI 1.36–2.54; \( P < 0.001 \)).

In a clinical study by Lin et al. [18], a total of 106 patients were enrolled (83 men). The mean age was 61 ± 16 years, mean LVEF was 35 ± 9% and mean NYHA functional class was 2. Log galectin-3 was significantly correlated with log N-terminal propeptide of type III procollagen (PIII-NP) (\( P = 0.006 \)), log tissue inhibitor of metalloproteinase-1 (TIMP-1) (\( P = 0.025 \)), log matrix metalloproteinase-2 (MMP-2) (\( P = 0.016 \)) and NYHA functional class (\( P = 0.034 \)), but not age, sex or LVEF. After adjusting for age, sex, smoking status and LVEF, the relationship between galectin-3 and extracellular matrix turnover biomarkers (including PIII-NP, TIMP and MMP-2) remained significant. After adjusting for age, sex, smoking status and NYHA functional class, the relationship between galectin-3 and PIII-NP or MMP-2 remained significant.

An interesting study by Milting et al. [19] described the kinetics of galectin-3 in 55 patients with end-stage HF with the need for mechanical circulatory support. This study determined that fibrosis-related biomarkers, including galectin-3, were increased compared with controls; that where there was no reduction of galectin-3 concentration by mechanical circulatory support only loading-related biomarker BNP was reduced; and that patients who did not survive on mechanical circulatory support, had a higher baseline galectin-3 concentration.

Galectin-3 and natriuretic biomarkers of heart failure

Shah et al. [11], in an evaluation of acute HF, found that combining plasma galectin-3 and BNP concentrations increased prognostic value over either biomarker alone (receiver operating characteristic analysis, \( P = 0.05 \)). In the DEAL-HF study [12], galectin-3 concentrations were also increased in patients with higher NT-proBNP concentrations (\( r = 0.265; P < 0.001 \)). In the PROVE IT-TIMI 22 study [15,16], when BNP was added to the model of HF development, the relationship between galectin-3 and HF was attenuated (adjusted OR 1.3, 95% CI 0.96–1.9; \( P = 0.08 \)).

In the PROVE IT-TIMI 22 study [13], galectin-3 did not significantly correlate with BNP (Spearman’s \( P = 0.13; P = 0.08 \)). When both BNP and galectin-3 were included in the multivariable model, however, the graded relationship between galectin-3 and HF was attenuated (adjusted OR 1.3, 95% CI 0.96–1.9; \( P = 0.08 \)). When patients were stratified by both galectin-3 at the median and BNP at the cut-off point of 80 pg/mL, patients with increased galectin-3 and BNP had the highest odds of HF: OR 4.7 (95% CI 1.7–13.0; \( P = 0.002 \)) for high BNP/high galectin-3 compared with the referent of low BNP/low galectin-3.

However, in multivariable modelling and univariate analysis in the HF-ACTION study [16], galectin-3 was not a significant predictor of cardiovascular death or cardiovascular hospitalization after the further addition of NT-proBNP (HR 0.97; \( P = 0.36 \)). For all-cause mortality, galectin-3 was not significant after further adjustment for NT-proBNP (adjusted HR 1.06; \( P = 0.30 \)).

Galectin-3—a promising target in HF therapy?

The direct inhibition of galectin-3 is possible by N-acetyl-
serine-aspartyl-lysyl-proline (Ac-SDKP), a naturally occurring tetrapeptide that prevents and reverses inflammation and collagen deposition in the heart in hypertension and HF after myocardial infarction. In the present study, we hypothesize that Ac-SDKP prevents galectin-3-induced cardiac inflammation, remodelling and dysfunction and that these effects are mediated by the transforming growth factor signalling pathway. Ac-SDKP prevents cardiac remodelling and dysfunction induced by galectin-3, a mammalian adhesion/growth-
regulatory lectin [6,20].

The impact of statins on galectin-3 concentration was shown in the CORONA study [21]: 1492 patients aged >60 years were included, with chronic HF of ischaemic cause, in NYHA class II–IV and with LVEF <40% (±35% if NYHA II). The patients were randomly assigned to rosuvastatin 10 mg/day or placebo. Galectin-3 was measured in plasma. The primary outcome was cardiovascular death, myocardial infarction or stroke. Of 1492 patients, 411 had a primary event during a median follow-up of 32.8 months. There was an interaction between baseline galectin-3 concentration and rosuvastatin on the primary endpoint (\( P \) value for interaction = 0.036). Among patients with below median plasma concentrations of galectin-3 (\( \leq 19.0 \) ng/mL), those assigned to rosuvastatin had a lower primary event rate (HR 0.65, 95% CI 0.46–0.92; \( P = 0.014 \)), lower total mortality (HR 0.70, 95% CI 0.50–0.98; \( P = 0.038 \)) and a lower event rate for all-cause mortality and HF hospitalizations (HR 0.72, 95% CI 0.54–0.98; \( P = 0.017 \)) compared with placebo, but no benefit was observed in patients with higher concentrations of galectin-3. The combination of concurrently low concentrations of galectin-3 and NT-proBNP (102.7 pmol/L) identified patients with a large benefit with rosuvastatin (HR 0.33, 95% CI 0.16–0.67; \( P = 0.002 \)) in the CORONA study [21]. Patients with systolic HF of ischaemic aetiology who have galectin-3 concentrations \( \leq 19.0 \) ng/mL may benefit from rosuvastatin treatment. However, the data from this post hoc analysis should be interpreted with caution as the overall results of the CORONA study did not show a significant effect on the primary endpoint.

According to data from clinical studies, measurement of galectin-3 concentration can be integrated into the management of patients with chronic HF [22,23]. For individuals with a galectin-3 concentration \( \leq 17.8 \) ng/mL, continuation of usual care is suggested, with periodic outpatient follow-up visits; for those in the 17.9–25.9 ng/mL range which constitutes moderate risk, more intensified
care management is suggested, with possibly more frequent visits, medication monitoring and adjustment. Finally, for those with concentrations > 25.9 ng/mL or a doubling of galectin-3, there is a very high risk of hospitalization (28%) and death over 18 months (43%); accordingly, they should receive particular attention, with optimal care and advanced management strategies.

Conclusions

Galectin-3 is expressed in various tissues and cell types and is involved in many biological processes, such as cell-cell and cell-extracellular matrix adhesion, cell growth and differentiation, the cell cycle, signalling, apoptosis and angiogenesis. Consequently, galectin-3 is involved in the regulation of development and immune reactions.

An increased concentration of galectin-3 was found in the patients with chronic HF, regardless of aetiology and HF typology (with preserved or reduced ejection fraction), and in acute HF, hypertrophic hearts and aortic stenosis with systolic dysfunction. Galectin-3 concentration is probably correlated with age and renal failure, but not with echocardiographic and haemodynamic HF data. The specific galectin-3 pathway, underlining cardiac fibrosis, seems very promising for high-risk patient identification. Galectin-3 has a very high predictive value in terms of short- and long-term prognosis and an additive value to natriuretic peptide measurement. Complementary prospective studies are still needed to confirm its prognostic value and to determine the target population for combined biomarker analysis and, maybe in the future, for using galectin-3 as a target for HF therapy.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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