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Review

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Is galectin-3 a promoter of ventricular dysfunction?

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Abstract

Heart failure is nowadays a common condition associated with high mortality and increased healthcare-related costs. Over the years, the research on heart failure management has been extensive in order to better diagnose and treat the condition. Since the progression of left ventricular dysfunction is a consequence of myocardial inflammation, apopotosis, and fibrosis leading to myocardium remodelling, several molecules that are involved in the inflammation pathways have been explored as possible biomarkers for the condition. The study of biomarkers and their key roles in inflammation could allow early identification of patients with heart failure, improve prognostic assessment, and provide a target for future therapies. Among currently studied biomarkers, extensive research has been conducted on galectin-3, a galactoside-binding lectin, which is synthetised and secreted when cardiomyocytes and fibroblasts are submitted to mechanical stress. Accordingly, it has been hypothesised that galectin-3 could be a promoter of left ventricular dysfunction. Galectin-3 has been shown to mediate inflammation by several different pathways which are further detailed in the current review. Also, we aimed to provide a comprehensive overview of existing evidence on the utility of galectin-3 in clinical settings associated with heart failure.

Keywords: Galectin-3, biomarker, heart failure, dyspnea, ventricular dysfunction, ventricular remodelling

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Introduction

Heart failure (HF) is currently a major cause of morbidity and mortality worldwide, being associated with increased hospitalization rates and healthcare-related costs [1]. Myocardial injury, hemodynamic overload, genetic, neuro-hormonal changes and inflammatory processes contribute to myocardial remodelling and progression of left ventricular (LV) dysfunction [2]. The myocardial remodelling process begins by inflammation, followed by fibrosis [3], myocardial hypertrophy [4], apopotosis and myocardial necrosis [5,6], resulting in ventricular dysfunction. Traditional approaches to the diagnosis and treatment of HF rely on identifying the causes and on attempting to manage these causes, with favourable outcomes [7]. However, little progress has been made in terms of identifying a therapeutic strategy that targeted fibrosis directly. Despite the current lack of such treatment, studies have

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been made and data has begun to pool regarding certain factors that seem to be involved in the development of fibrosis and HF. Such molecules are currently in use or under study as biomarkers of HF, contributing to early diagnosis of the condition, beyond the already aknowledged N-terminal pro-Brain-type Natriuretic Peptide (NT-proBNP) [8]. Galectin-3 has been proposed as a biomarker of HF due to its active involvement in the inflammatory [9] and pro-fibrotic process [10,11], since its synthesis and secretion are triggered by mechanical stress on cardiomyocytes and fibroblasts. The possibility of inhibiting these links in the pathophysiological process of fibrosis development maintains the interest of researchers and clinicians willing to stop or even prevent the development and progression of HF [12-15].

The aim of this review is to provide a general outlook on the experimental and clinical data which are currently available regarding the role of galectin-3 in HF.

Galectin-3: Biological background and function

Among the members of this lectin family, galectin-3 has been the most extensively studied; galectin-3 has been shown to mediate several processes, including cell adhesion, migration, survival, death, and differentiation [16]. Galectins bind β-galactose-containing glycoconjugates and have similar primary structures in their carbohydrate recognition domains (CRDs) [17]. At least 15 members of the galectin familiy have been identified in animal experiments so far and most of them (galectin 1-4, 7-9, 12-13) have also been found in humans. The galectin family includes three subtypes: (i) prototype, (ii) chimera, and (iii) tandem repeat group, differentiated by the number and organization of CRDs [18]. Galectin-3 is a chimeric, soluble β-galactoside binding lectin from the galectin family, with three distinct domains: a NH2-terminal domain, a proline-rich collagen-alpha-like domain, and a COOH-terminal domain containing the CRD [16, 17, 18, 19]. The C-terminal domain allows binding to carbohydrate ligands, such as N-acetyllactosamine, while the N-terminal domain allows the formation of oligomers and interaction with cell mebranes or extracellular receptors, such as those found on macrophages or collagen IV, respectively [20, 21].

Galectin-3 is found under different forms: 1) the primary form contains a polypeptidic chain of 250 aminoacids; the N-terminal domain has 120 aminoacids and allows the formation of oligomers, as well as the expression of the molecule on the cell membrane [20]; the collagen-alpha-like medial sequence includes proline and glycine, and can be cleaved by metaloproteinases [22]; the C-terminal domain contains 130 aminoacids [23]; 2) in the secondary form, CRD is organized as a β-pleated sheet, with antiparallel organization of polypeptidic chains which render it flexible and resilient to stretch [24]; 3) a globular tertiary form; 4) a quaternary form that may be either mono- or multimeric according to the concentration: when concentrations are low, monomers are more likely to occur, promoting intercellular adhesion, by binding and blocking integrins on other cells; when concentrations are higher, multimers are formed, mediating intercellular adhesion.

Galectin-3 is coded by the LGALS3 gene on chromosome 14 [25] and can be found in different compartiments in the body, and under different forms. Galectin-3 can be found in several species, in the intracellular, as well as in the extracellular space [26]. These biomarkers are mostly found in the cytoplasm [27], but may also cross cellular and intracellular membranes, thus being able to enter the nucleus or mitochondria, to be expressed on the cell membrane or to pass into the extracellular space, and, subsequently, in the systemic circulation [27,28]. Cytosol galec-

tin-3 inhibits apoptosis, and can be expelled from the cell by exocytosis, circumventing the Golgi apparatus and the endoplasmic reticulum, further having a tendency to bind to several extracellular matrix proteins, such as fibronectin, tenascin and laminin [21]. In the nucleus, galectin-3 is involved in splicing and cell proliferation, while when expressed on the surface of the cells, it has the ability to modulate cell survival and mRNA splicing [29].

Galectin-3 mediates interactions between cells and between cells and the extracellular matrix, binds to glicans and modulates intracellular signaling pathways, leading to cell activation [30], proliferation and apoptosis [31]. Moreover, galectin-3 has an important proadhesion role [32], acting as a ligand for glucose, lipids and mycrobiological factors, including endotoxins [33]. Also, it has chemotactic properties, being involved in the recruitement of monocytes and macrophages, neutrophile adhesion, and the release of pro-inflammatory cytokines from leukocytes and mastocytes [34], as well as the phagocytic clearance of apoptotic neutrophiles [35].

Galectin-3 synthesis occurs in several types of cells, such as fibroblasts, granulocytes, tumoral cells and microglia. According to the synthesis site, galectin-3 is involved in organ-specific pathophysiology, modulating fibrogenesis [10,11] and inflammation [9] at these sites.

Galectin-3: role in cardiac remodelling

Galectins seem to have a wide range of biological roles, and evidence begins to pool that they are involved in inflammatory processes in several tissues and organs, including the heart.

Galectin-3 induces cardiac remodelling by several processes including myocardial cell apoptosis, hypertrophy, inflammation and fibrosis, leading to myocardial dysfunction (Figure 1).

Cell Apoptosis

Apoptosis preserves the balance between proliferation and turnover in all living tissues, including the myocardium. At this level, when cell stress occurs, galectin-3 activates the proapoptotic c-Jun-N-terminal kinase ½, triggering cell apoptosis by increasing deoxinucleotidil transpherase terminal 2'-deoxyuridine 5'-triphosphate [36]. Extracellular apoptosis induced by galectin-3 in activated T cells induces mithochondrial apoptosis, cytchrome C release and the activation of caspase-3 [37]. Endogenous galectin-3 is involved in apoptotic signalling pathways regulated by the activated caspase-8 and the pro-apoptotic activity of the mitochondria, inducing cell death [37]. The ability of galectin-3 to induce T cell apoptosis is dependent on its cytosolic levels [37].

Cellular mechanisms

Cell adhesion is necessary for maintaining the three-dimensional structure and normal function of the heart. Galectin-3 promotes neutrophil and laminin adhesion and mediates IL-8 synthesis and L-selectin shedding to induce appropriate immune responses [38]. Also, galectin-3 can bind monocytes to laminin and contribute to their activation, as well as up-regulate the expression of other adhesion mollecules and increase cell adhesion to fibronectin [39]. Further studies have shown that endogenous galectin-3 favours cell adhesion to collagen IV, while exogenous galectin-3 accelerates epitelial healing processes and promotes cell migration [39].

Myocardial inflammation

Acute myocardial inflammation is a normal defensive response to lesions, irritation and infections, while chronic inflammation is associated with deleterious effects. Chronic inflammation occurs either due to failure of acute inflammation processes in completing the healing process, or by persistence of the harming agent.

Galectin-3 is an inflammatory protein which activates and promotes macrophage migration [40]. Galectin-3 mollecules expressed by eosinophils bind to immobilized galectin-3 and type 1 vascular adhesion cells [40]. In patients with HF, increased galectin-3 expression promotes neutrophile recruitement at the inflammation site [40].

Myocardial fibrosis

Myocardial fibrosis is considered irreversible in a wide range of cardiovascular diseases, including overt HF [41]. Recent studies have shown that galectin-3 is involved in the proliferation and differentiation of myofibroblasts that further stimulate collagen synthesis. Galectin-3 expression is elevated in homozygote TGRm-Ren2-27 transgenic rats who develop HF and is colocalized on the surface of activated macrophages, being able to bind to fibroblasts and the extracellular matrix [42]. Moreover, the proliferation of fibroblasts induced by recombinant galectin-3 leads to collagen synthesis [42]. Galectin-3 seems to be involved in myocardial inflammation by both macrophage activation and by increased proliferation of extracellular matrix producing cells.

To conclude, cytosolic, nuclear and circulating galectin-3 is involved in preserving the balance between proliferation and apoptosis, thus promoting the normal turnover of several types of cells, including the myocytes. Moreover, galectin-3 promotes normal healing after acute inflammation. However, when cells are chronically submitted to stress, galectin-3 related pathways promote the development of myocardial hypertrophy and fibrosis. (Figure 1)

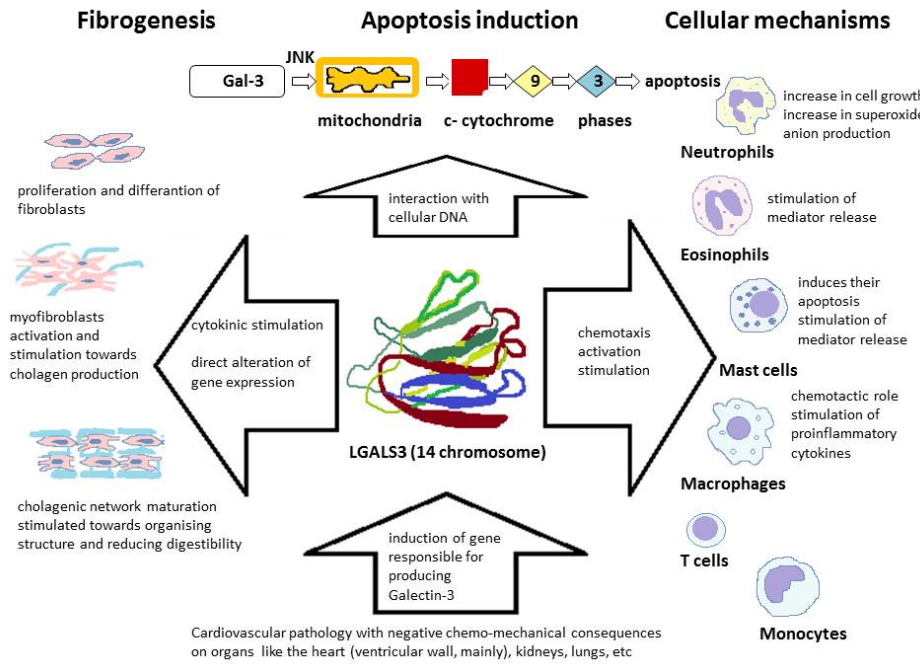

Figure 1. Galectin-3 in cardiac remodelling – mechanically-induced stress on myocytes and fibroblasts triggers increased synthesis and secretion of galectin-3. Further, galectin-3 modulates fibrogenesis by cytokine stimulation and direct alteration of gene expression; induces apoptosis by interaction with cellular DNA; and contributes to the chemotaxis, activation and stimulation of all white blood cells.

Galectin-3 in experimental studies

Several experimental studies have demonstrated the involvement of galectin-3 in inflammation, fibrogenesis and the development of vascular and myocardial remodelling and dysfunction. Also, some researchers attempted to limit or prevent myocardial fibrosis by targeting galectin-3.

Sharma et al, for instance, showed that repeated intrapericardial infusions with galectin-3 lead to collagen accumulation, myocardial remodelling and ventricular dysfunction in previously healthy rodents [9].

Also, in a relatively recent study, both wild-type and galectin-3 knock-out mice were submitted to angiotensin II infusions and transverse aortic constriction for 28 days in order to induce cardiac remodelling. Mice in both groups developed myocardial hypertrophy, but only wild-type mice had evidence of myocardial fibrosis, while galectin-3 knock-out mice did not. Accordingly, the authors studied the effects of a galectin-3 inhibitor, N-acetyl lactosamine, on both cultured cells and rats, showing less myocardial remodelling after treatment [43]. Moreover, Frenay et al. demonstrated the protective effect of N-acetyl lactosamine on renal function in hypertensive rats, showing decreased proteinuria and plasma creatinine, as well as lower systolic blood pressure values, despite persistently elevated matrix remodelling factors [44].

In another study, arterial hypertension was induced in both wild-type and galectin-3 knock-out Wistar rats by the administration of aldosterone and salt, but only the wild-type rats had increased aortic galectin-3 expression, inflammation, and collagen type I. These effects seemed preventable or reversible if citrus pectin – a galectin-3 inhibitor – and/or spironolactone were administered. Aortic mRNA analysis revealed that interleukin-6 synthesis was considerably diminished by spironolactone and completely blocked by citrus pectin [45]. These results may provide a pathophysiological background for the already documented reverse-remodelling effects of spironolactone in human patients with HF and raise hope for potential therapeutic effects of citrus pectin.

Also, myocardial hypertrophy and cardiac remodelling with increased fibrosis were associated with high galectin-3 levels in rats with induced autoimmune myocarditis, and were shown to respond to treatment with T-3999, a novel phenylpyridazinone [46].

Other animal studies explored the pro-inflammatory potential of galectin-3 in other tissues. For example, Dvorankova et al. demonstrated that in vitro administration of recombinant galectin-3 can trigger activation of myofibroblasts, with subsequent production of extracellular matrix, a finding which could be used in tissue engineering and wound repair [47]. Henderson et al. explored the involvement of galectin-3 in the development of liver fibrosis, showing that myofibroblast activation and procollagen (I) expression is markedly reduced when the galectin-3 gene is supressed [48]. Also, kidney fibrosis is unlikely to occur in the absence of galectin-3 [49].

Galectin-3 in clinical studies

During the last few years, galectin-3 has raised the interest of clinical researchers, and, accordingly, several clinical studies were conducted in order to explore the use of galectin-3 in clinical practice for the purpose of diagnosis, risk-stratification, monitoring the response to therapy or establishing prognosis (Table 1).

Diagnostic use

The diagnostic use of galectin-3 has been explored in several large trials, as well as smaller studies, yielding somewhat conflicting results.

Table 1. Prognostic value of galectin-3 in clinicial studies

Study	Inclusion criteria	No. of patients	Cut-off value	Duration of follow-up	End points	Correlation to outcomes	Additional value to BNP or NT-proBNP
PRIDE [50]	Patients with dyspnea presenting to the emergency service	599	14.97 ng/mL	60 days	Death Death or readmission	Predictor of mortality or the combination of death/recurrent HF within 60 days	The combined use of galectin-3 with NT-proBNP was the best predictor for prognosis in patients with acute HF.
VAL-HEFT [56]	Stable NYHA II-IV LVEF <40% LV internal diastolic dimension/ body surface area > 2.9 cm/m^2	1650	16.2 ng/mL	23 months	Primary end-points: all-cause mortality and the first morbid event (death/sudden death with resuscitation/ hospitalization for HF/ administration of inotropic or vasodilator drug for ≥ 4hours without hospitalization) Secondary end-point: hospitalization for HF	Valsartan reduced hospitalizations for HF in patients with low galectin-3 baseline levels	Additive value when used with NT-proBNP for all-cause mortality and hospitalization for HF
Aldo-HF [51]	Class NYHA II-III symptoms LVEF ≥50% at rest Grade ≥1 diastolic dysfunction or atrial fibrillation Peak VO_2 ≤ 25 mL/ kgc/min	377	12.1 ng/mL	12 months	Change in peak VO_2 and Change in E/E' at 12 months after randomization	No changes in peak VO_2 E/E' ratio decreased in the spironolactone group; lost after adjustment for confounding factors	NA
RELAX [59]	HFpEF	208	Tertiles galectin-3 (ng/mL): < 12.17 12.17–15.90 > 15.90	6 months of therapy	Response to therapy with sildenafil (change in peak oxygen consumption)	No correlation with response to therapy	NA

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Study	Inclusion criteria	No. of patients	Cut-off value	Duration of follow-up	End points	Correlation to outcomes	Additional value to BNP or NT-proBNP
PROVE-IT TIMI 22 [15]	200 patients with acute coronary syndromes – 100 patients hospitalized for HF vs. anage and sex matched matched group of patients without hospitalization for HF	200	**Median(µg/L):** 16.7 **Quartiles (µg/L):** <13 13.0-15.5 15.6-19.2 >19.2	2 years	Hospitalization for new or worsening HF	Galectin-3 levels are associated to the risk of developping HF	Elevated levels of both galectin-3 and BNP had the highest odds of heart failure. Galectin-3 and BNP levels were NOT significantly correlated.
CARE-HF [12]	Class III/IV NYHA patients undergoing CRT	260 (132 with CRT; 128 controls)	30 ng/mL	18 months	Survival without unplanned hospitalization for HF Survival and LVEF >35% after CRT Survival and NT-proBNP <1000 ng/L	No predictive value for LVEF >35% after CRT Correlated to survival and hospitalization for HF, and survival and NT-proBNP <1000 ng/L (non-significant after adjustment for eGFR)	NA
MADIT-CRT [60]	NYHA I/II, coronary artery disease, LVEF ≤30% OR NYHA II, non-ischemic dilated cardiomyopathy, QRS ≥130 msec	654 (386 CRT-D; 268 ICD only)	**Quartiles (ng/mL):** 20 (17.2-22.0); 27.1(25.4-29.0); 36.7 (33.7-39.9); 53.6 (47.4-64.0).	12 months	Nonfatal HF event or death (first of any event)	Reduced rate of non-fatal HF events or death in patients with the highest galectin-3 levels Higher benefit in the CRT-D group vs. the ICD only group	NA Weak correlations to BNP at baseline evaluation

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Study	Inclusion criteria	No. of patients	Cut-off value	Duration of follow-up	End points	Correlation to outcomes	Additional value to BNP or NT-proBNP
COACH [14]	Patients with chronic HF	592	**Quartiles (ng/mL):** 5.0–15.2 15.2–20.0 20.0–25.9 25.9–66.6	18 months	Rehospitalization for HFor death	Better prognostic value in patients with HF and preserved ejection fraction	Combining plasma galectin-3 and BNP levels increased prognostic value over either biomarker alone
CORONA [55]	Patients > 60 years of age, coronary artery disease and HF with reduced ejection fraction (<45%)	1462	19 ng/mL	32.8 months	Cardio-vascular mortality Myocardial infarction Stroke	Patients with lower galectin-3 levels have more benefit from rosuvastatin therapy	Combined use of NT-proBNP (cut-off 868 pg/mL) and galectin-3, or C-reactive protein (cut-off 2 mg/L) and galectin-3 identifies patients who are likely to benefit from rosuvastatin therapy
HF-ACTION [66]	HF NYHA II-IV; LVEF ≤35%	895	14 ng/mL	2.5 years	Primary outcome: all cause hospitalization, all cause mortality. Secondary outcome: cardio-vascular death or cardio-vascular hospitalization; car-dio-vascular death or HF hospi-talization; all cause mortality	Lower levels correlated with prolonged hospitalization-free survival	No additive value No longer correlates to hospitalization-free survival after adjustment for NT-proBNP
PREVEND [67]	Volunteers from the general population	7968	**Median (ng/mL):** 10.9 **Quintiles (ng/mL):** 7.7 (7.0–8.2); 9.4 (9.0-9.8); 10.9 (10.5-11.3); 12.6 (12.2-13.1); 15.6 (14.5-17.7)	10 years	All-cause mortality Cardiovascular death	Predicts all-cause mortality No ability to predict cardiovascular mortality or neoplasia-related mortality	No longer predicted cardio-vascular mortality after adjustment for NT-proBNP.

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Study	Inclusion criteria	No. of patients	Cut-off value	Duration of follow-up	End points	Correlation to outcomes	Additional value to BNP or NT-proBNP
DEAL-HF [10]	Patients with chronic HF (NYHA class III or IV)	232	**Median (ng/mL):** 17.72 (best sensitivity and specificity) **Quartiles (ng/mL):** <13.63; 13.63–17.63; 17.64–21.62; >21.62.	6.5/8.7 years	All-cause mortality and hospitalization for HF and the duration of the study (at 12 months) Vital status on long term	Galectin-3 is an independent predictor of mortality	Highest mortality in patients with high galectin-3 and NT-proBNP levels
The Framingham Offspring Cohort [68]	General population	3353	**Quartiles (ng/mL) Men:** 13.9–11.1; 11.1–13.1; 13.1–15.4; 15.4–47.7. **Quartiles (ng/mL) Women:** 5.0–12.0; 12.0–14.3; 14.3–16.8; 16.8–52.1.	8.1 years	All-cause mortality Incident HF	Correlated to the risk of death and incident HF	No

HF, heart failure; LV, left ventricle; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PRIDE, Pro-BNP Investigation of Dyspnea in the Emergency Department; Val-HEFT, Valsartan Heart Failure Trial; Aldo HF, Aldosterone Receptor Blockade in Diastolic Heart Failure; RELAX, PhosphodiesteRasE-5 Inhibition to Improve CLinical Status And EXercise Capacity in Diastolic Heart Failure; PROVE IT TIMI, Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22; CARE HF, Cardiac Resynchronization in Heart Failure; MADIT CRT, Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy; COACH, Coordinating study evaluating Outcomes of Advising and Counseling in Heart failure; CORONA, Controlled Rosuvastatin Multinational Trial in Heart Failure; HF-ACTION, A Controlled Trial Investigating Outcomes of Exercise TraiNing; PREVEND, Prevention of REnal and Vascular END stage disease.

Valuable data have been obtained from the PRIDE (Pro-BNP Investigation of Dyspnea in the Emergency Department) trial, which tested the diagnostic and prognostic abilities of NT-proBNP, galectin-3 and apelin in acute HF. In this trial, galectin-3 was proved superior to apelin, but inferior to NT-proBNP for identifying acute HF, despite having better prognostic value [50].

In the Aldo-DHF (Aldosterone Receptor Blockade in Diastolic Heart Failure) trial, focused on patients with HF with preserved ejection fraction (HFpEF), galectin-3 was inversely correlated to exertion capacity, assessed by the 6-minute walk test distance and peak oxygen consumption, the quality of life, assessed by the Short Form 36, and worse outcomes [51].

In the research conducted by Mueller et al, comparing the ability of BNP, sST2 and galectin-3 for identifying HF patiens, the latter performed the least well, having the lowest area under the curve, and did not provide any additional diagnostic value to BNP [52].

Mohammed et al. explored the diagnostic value of galectin-3 in a pediatric population with HF and acyanotic congenital heart disease and demonstrated statistically significant correlations between galectin-3 levels and HF severity. Their analysis yielded 83.3% sensitivity and 63.3% specificity for predicting HF, as well as significant direct correlations to left atrial and LV diameters or pulmonary artery pressures; negative correlations to the LV ejection fraction (LVEF) and shortening fraction also emerged [53]. In this study, however, acknowledged biomarkers of HF such as BNP or NT-proBNP have not been used and, therefore, it is not known whether galectin-3 could be superior or provide any additional value to conventional biomarkers.

Considering the results of these studies, galectin-3 is not reliable enough to identify patients with HF and does provide significant additional diagnostic value when used in combination with NT-proBNP.

Impact of medical therapy on galectin-3 levels

Correlations between galectin-3 and medical, interventional or device therapy outcomes have been approached in some large studies.

In the GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiaca) [54] and CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) trials [55] patients with HF did not seem to benefit from rosuvastatin therapy, beyond a reduction in the rate of hospitalization [55]. However, Gullestad et al. analyzed a subgroup from the CORONA trial and showed that selected patients with low levels of galectin-3 (<19 pg/mL) responded well to rosuvastatin therapy, having lower cardiovascular mortality, myocardial infarction or stroke rates, and that benefits were highest in patients who had both low galectin-3 and NT-proBNP, or C-reactive protein levels [13].

Low galectin-3 levels also emerged as a good predictor of response to valsartan therapy in a subgroup analysis of 1650 patients from the Val-HEFT (Valsartan Heart Failure Trial) trial, independently of any other factors, including NT-proBNP levels. In this study, patients with galectin-3 levels lower than the median value of 16.2 ng/mL had significantly fewer hospitalizations for HF, while those with higher galectin-3 levels did not benefit at all from valsartan therapy [56].

By contrast, galectin-3 levels did not predict response to either spironolactone [57] or sildenafil [58] therapy in patients with HFpEF. Considering the fact that spironolactone has not been proved to influence outcomes in HFpEF patients beyond reducing hospitalization for HF and increasing the risk of hyperkaliemia [59], and the use of sildenafil in clinical practice is not endorsed by current HF guidelines, the importance of these findings is limited.

Galectin-3 and device-based therapy

Data regarding the utility of galectin-3 in patients with cardiac resynchronization therapy (CRT) has also begun to pool. Interestingly, in a substudy of the MADIT-CRT (Multicenter Automatic Defibrillator Implantation with Cardiac Resynchronization Therapy) trial on patients with New York Heart Association (NYHA) class I/II undergoing CRT-D, higher levels of galectin-3 at baseline were associated with better outcomes (lower rate of non-fatal HF events or death) [60]. In this cohort, higher galectin-3 levels may suggest the presence of metabolically active myocardial fibrogenesis, that is likely to regress after CRT, leading to reverse remodelling, thus explaining the higher benefit in the increased galectin-3 levels quartile.

By contrast, in the CARE-HF study, higher galectin-3 levels were associated with worse outcomes, but, in this trial, patients were included if they had NYHA III-IV symptoms [12] and might have been beyond active inflammation.

In a relatively small study of 55 patients with advanced HF who received circulatory support devices (LV assist devices or total artificial hearts), galectin-3 levels were higher than in healthy volunteers, and were not significantly changed in the critically ill patients after a month of follow-up [61]. However, higher levels of galectin-3 were correlated with increased mortality after LV assist device implantation [61].

These findings were further confirmed in another study on 151 patients who received a LV assist device [62].

In the study by Cormilas et al, galectin-3 levels were measured in patients with either stable HF (defined as class NYHA I-III) or severe (class IV NYHA) HF, among whom 63 received a LV assist device, and 23 were explanted during the follow-up period; the study also included 85 patients who had a heart transplant. In this study, galectin-3 levels were correlated to increased HF severity and were associated with lower survival after LV assist device placement, as well as with a higher incidence of coronary allograft vasculopathy after transplantation. Moreover, in this research, galectin-3 levels were lower after transplantation and higher after LV assist device explantation, suggesting a deleterious effect of the latter, probably related to the progression of inflammation in this setting [63].

Prognostic value in heart failure

Short term prognosis

The short-term prognostic value of galectin-3 was proved in the PRIDE trial, which showed an increased area under the curve for mortality at 60 days, even by comparison with NT-proBNP. However, prognosis was best assessed when both biomarkers were used [64].

In a recent study, galectin-3 levels were associated with worse prognosis after transcatheter aortic valve implantation at 30 days, but also on the long-term [65].

In the study by Mueller et al., galectin-3 predicted one year all-cause mortality as accurately as BNP and soluble ST2 in patients with acute HF. The combined use of every two biomarkers did not improve the prognostic ability for all-cause mortality at one year [52].

Medium term prognosis

In the COACH (Coordinating study evaluating Outcomes of Advising and Counseling in Heart failure) trial, 592 patients with different degrees of HF were included, and a combined primary end-point of all cause mortality and HF hospitalization was followed. Galectin-3 levels at 6 months did not provide any additional value to baseline levels for prognostic purposes, suggesting that a single determination may be sufficient. In addition to that, the combined use of galectin-3 and NT-proBNP provided incremental prognostic value to either biomarker alone. Also, galectin-3 was signficantly higher in

patients with HFpEF (defined as LVEF>40%), by comparison with patients with reduced LVEF, and might therefore be of a particular use in this category [14].

Moreover, in the CARE-HF (Cardiac Resynchronization in Heart Failure) trial, increased galectin-3 levels at enrollement predicted mortality and HF hospitalization in patients with III-IV NYHA class HF, reduced LVEF and ventricular dyssynchrony [12].

The ability of galectin-3 to predict outcomes in patients with acute coronary syndromes was evaluated in a nested case-control study on 100 patients from the TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis In Myocardial Infarction 22) trial. These patients were followed for 2 years and the main finding was that increased galectin-3 levels in the acute setting were associated with the development of HF in patients with acute coronary syndromes [15].

The HF-ACTION (A Controlled Trial Investigating Outcomes of Exercise TraiNing) trial was conducted on 885 chronic HF patients with reduced ejection fraction (HFrEF) who were followed for 2.5 years. In this trial, galectin-3 levels correlated with the NYHA class, maximum oxygen consumption, systolic blood pressure and the risk for hospitalization or all-cause mortality, in univariate analysis; however, the correlation was lost in multivariate analysis, when adjustments for NT-proBNP levels were made [66].

Long-term prognosis

Several studies also approched the long-term prognostic value of galectin-3.

Among these, the PREVEND (Prevention of REnal and Vascular END stage disease) trial, performed on healthy volunteers who were followed over 10 years, showed that galectin-3 was an independent predictor of death of cardiovascular causes [67].

The Framingham Offspring Cohort included 3,353 patients who were followed-up for 8.1 years; in these patients, higher galectin-3 levels at enrollement were associated with an increased risk for HF, even after adjustment for BNP and clinical variables. Also, galectin-3 levels were associated with increased all-cause mortality [68]. In the study by Shah et al., elevated galectin-3 levels were also associated with increased mortality at 4 years [54].

Similarly, in the DEAL-HF trial on 232 NYHA III/IV HF patients, survival was significantly higher in the group with lower galectin-3 levels (<17.72 ng/mL), during the 6.5 years follow-up [10]. After extending the follow-up period to 8.7 years, galectin-3 levels were positively associated with the risk of death. However, in this study, galectin-3 levels were correlated to the progressive impairment of the renal function, rather than to parameters of LV remodelling such as increased end-diastolic volumes [10]. (Table 1)

Confounding factors

The study of biomarkers of HF has among its aims the identification of a biomarker with high specificity that would not be significantly influenced by co-morbidities. Data regarding galectin-3 suggests, however, that it can be altered by several other factors [13] [51] [61] [63]. Among possible confounders, the most solid evidence was gathered regarding the impaired renal function [13] [51] [61] [63]. Beside the renal function, other confounders have been identified, including older age, female gender, hypertension, body mass index, or prevalent coronary heart disease [13] [68].

The value of galectin-3 in clinical practice. Future perspectives

Galectin-3 is currently one of the most widely investigated biomarkers for cardiovascular

disease, after BNP and NT-proBNP. However, the results that have been derived so far from experimental as well as clinical studies are somewhat conflicting and cannot provide any guidelines regarding the use of this molecule in clinical practice. Further research is needed before implementing the routine assessment of galectin-3 in cardiology, as well as in other specialities. Despite the present lack of convincing evidence from large trials, the study of galectin-3 remains a topic of interest for researchers and clinicians alike, as it does seem to have some diagnostic and prognostic value. Moreover, due to its role in inflammation, myofibrobalst activation, as well as in the synthesis and accumulation of collagen, galectin-3 may become a therapeutical target for preventing and limiting the development of myocardial fibrosis. Further, more extensive research is needed to reach that goal.

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Abbreviations

Aldo-HF, Aldosteron Receptor Blockade in Diastolic Heart Failure
CARE-HF, Cardiac Resynchronization in Heart Failure
COACH, Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure
CORONA, Controlled Rosuvastatin Multinational Trial in Heart Failure
CRDs, carbohydrate recognition domains
CRT, cardiac resynchronization therapy
GISSI-HF, Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiaca
HF, heart failure
HF-ACTION, A Controlled Trial Investigating Outcomes of Exercise TraiNing
HFpEF, heart failure with preserved ejection fraction
LV, left ventricle
LVEF, left ventricular ejection fraction
NT-proBNP, N-terminal pro-Brain-type Natriuretic Peptide
NYHA, New York Heart Association
PREVEND, Prevention of Renal and Vascular END stage disease
PRIDE, Pro-BNP Investigation of Dyspnea in the Emergency Department
PROVE IT TIMI 22, Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis In Myocardial infarction 22
RV, right ventricle
Val-HEFT, Valsartan Heart Failure Trial

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