Galectin-3 in Heart Failure

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Galectin-3 in Heart Failure
An Update of the Last 3 Years

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KEYWORDS

• Galectin-3 • Heart failure • Fibrosis • Galectin-3 inhibitor • Biomarker • Prognosis

KEY POINTS

- Galectin-3 is a pleiotropic protein that is produced after organ injury and secreted in the systemic circulation.
- Galectin-3 is an established biomarker and, in a recent meta-analysis comprising 32,350 participants with a total of 323090 person-years of follow-up, galectin-3 was associated with all-cause and cardiovascular mortality.
- Galectin-3 is a protein with important biological functions, especially fibrosis formation, and as such is currently explored as a potential target for therapy.

INTRODUCTION

This article provides an update regarding the most recent published literature on galectin-3 as a biomarker in heart failure (HF) and gives an outlook toward its use as a biotarget.[1] In the last decade, several reviews from our group and others have summarized the articles on galectin-3 as an HF biomarker.[2–8] The authors have included articles extracted from the PubMed library up to April 2017.

HF is an important cause of morbidity and mortality in the Western world and approximately 10% of the people more than 70 years of age are diagnosed with HF.[9] Despite considerable advances in diagnosis and management of HF, 5-year mortality still remains around 50%, which is extremely high. The prevalence of HF is globally increasing, mainly because of the aging population[10] and increased success rates in treating cardiovascular diseases that precede HF, including myocardial infarction (MI) and hypertension.

HF is also an expensive disorder, often requiring periods of hospitalization, and this adds significantly to the burden of disease. According to an estimation, the annual cost of HF in the United States will increase from US$31 billion to US$70 billion by 2030.[11] Therefore, avoiding unnecessary HF hospitalizations is a top priority in HF management.

Patients with HF usually present with the clinical symptoms of fatigue, as well as shortness of breath and peripheral edema, which result from insufficient cardiac function. The authors use the term HF for the early stage of the disease even when clinical symptoms may not yet be present. According to the 2016 European Society of Cardiology (ESC) guidelines, HF is classified as either HF with preserved ejection fraction (HFpEF; ie, EF $\geq$ 50%), HF with midrange ejection fraction

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(HFmrEF; EF 40%–49%), and HF with reduced ejection fraction (HFrEF; EF<40%).[12] Different underlying disorders lead to the development of HF, as described elsewhere.[12–14]

Biomarkers reflect pathophysiologic mechanisms occurring in the body and are usually used as adjuncts in patient management. As such, biomarkers may find their utility in HF diagnosis, prognosis, and risk stratification; although their use in HF has expanded rapidly, several biomarkers have still not made their way into regular patient management. Current HF guidelines focus primarily on B-type natriuretic peptide (BNP) or its biologically inert amino-terminal pro-peptide, N-terminal proBNP (NT-proBNP).[12] However, NT-proBNP usage has limitations: Although NT-proBNP levels can be used to diagnose both types of HF, low levels might not exclude HFpEF diagnosis.[15]

The 2013 American College of Cardiology Foundation/American Heart Association guideline for the management of HF recommends the use of galectin-3 for risk stratification as well as for prognosis in patients with moderate and severe HF (class IIb).[16] Although current ESC guidelines on HF do not recommend galectin-3 for clinical practice, it seems to be a useful biomarker in various settings, which are discussed later.

Galectin-3 is one of 14 members of the lectin family and is encoded by a single gene (LGALS3); it binds various β-galactosides using its carbohydrate recognition domain (CRD), and elicits several biological effects. The CRD consists of approximately 130 amino acids and is indicated in the pathophysiology of HF. Galectin-3 also plays an important role in inflammation; tissue repair, including fibrogenesis; as well as cardiac ventricular remodeling, which is an important hallmark in HF[2,14,17] (**Fig. 1**).

This article discusses the utility of galectin-3 in new-onset, acute, and chronic HF, including HFrEF and HFpEF. First, it highlights different diagnostic assays and reference ranges of galectin-3 in various populations.

GALECTIN-3 ASSAYS

Establishing a reproducible and accurate method to measure galectin-3 in the circulation is important for research as well as in clinics and there are several commercial galectin-3 assays that provide an accurate measurement of circulating galectin-3. The most commonly used galectin-3 assays are summarized in **Table 1**. These assays can be used to detect galectin-3 from venous blood samples, which can be collected in EDTA (ethylenediaminetetraacetic acid) tubes or in serum. After separation, the serum or plasma may be stored at −70°C for approximately 10 years and can undergo up to 9 freeze-thaw cycles without significantly influencing galectin-3 test results.[18] The BG Medicine (BGM) galectin-3 enzyme-linked immunosorbent assay (ELISA) kit and R&D ELISA kit are manual assays, whereas

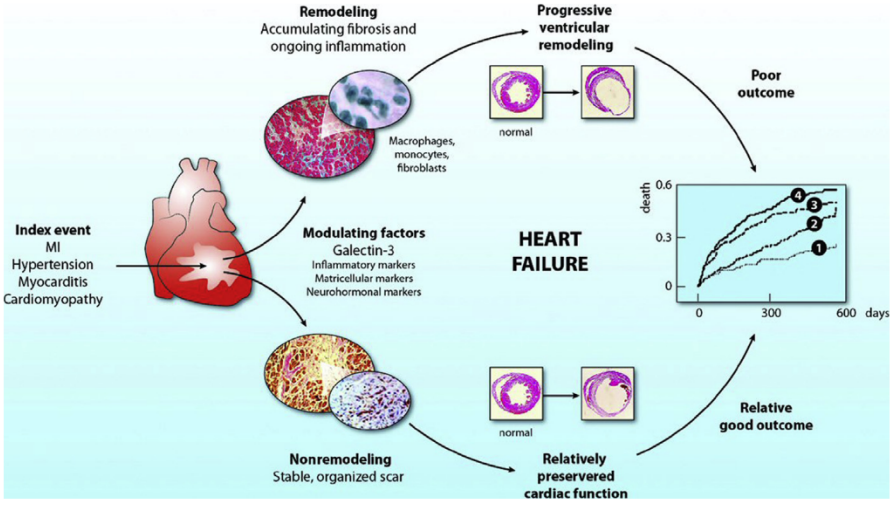

Fig. 1. Mechanism underlying HF. An index event such as a MI, endocarditis, or long-standing hypertension causes stress to the heart. This index event provokes a release of different cytokines that may cause a pathologic remodeling with an upregulation in fibrosis and inflammation; on-going pathologic remodeling leads to a poor outcome with an increased mortality. In contrast, there can be a nonremodeling with a stable and organized scar and a relatively preserved cardiac function. (*From* de Boer RA, Meissner M, van Veldhuisen DJ. Galectin-3. In: Maisel AS, editor. New Delhi (India): Jaypee Brothers, 2012. p. 206; with permission.)

Table 1
Comparison of galectin-3 assays

			Total Imprecisions		Detection Limit								
	Sample Volume (μL)	Duration (h)	Intravariability In CV (%)	Intervariability In CV (%)	LoB (ng/mL)	LoD (ng/mL)	LoQ (ng/mL)	Measuring Range (ng/mL)	Interference	Cross Reactivity	Percentiles[d]		
BGM	30	3.5	3.2	5.6	0.86	1.13	1.32	1.4–94.8	[b]	[c]	19	22.1	26.2
ARCHITECT: Stat	25[a]	18	3.4	4.1	0.8	1	4	4–114	[b]	[c]	22.4	25.7	27.5
ARCHITECT: Routine	25[a]	28	4.1	4.9	0.8	1	4	4–114	[b]	[c]	22.4	25.7	27.5
VIDAS	200	20	1.3	5.5	2.2	2.4	3.3	3.3–100	[b]	[c]	—	—	—
R and D	50	4.5	3.9	5.9	—	0.02	—	0.313–10	[b]	[c]	9.1	9.9	10.6
Alere	10	—	12	5	—	—	—	0.5–86.2	[b]	[c]	—	—	—

Abbreviations: BGM, BG Medicine; CV, cardiovascular; LoB, limit of blank; LoD, limit of detection; LoQ, limit of quantification.

[a] Plus 50 μL of dead volume.

[b] No interference with conjugated bilirubin; unconjugated bilirubin; lipidemia; triglycerides; bovine serum albumin; cholesterol; creatinine; hemoglobin; galectins 1, 2, 4, 7, 8, 9, 10, 14; MAC-2BP and commonly used cardiovascular medication. Interference with hemolyzed samples, human antimouse antibody, rheumatoid factor, and verapamil.

[c] No cross reactivity with collagens I, III, and 9, and other galectins.

[d] Percentiles based on general population.

From Meijers WC, van der Velde AR, de Boer RA. The ARCHITECT galectin-3 assay: comparison with other automated and manual assays for the measurement of circulating galectin-3 levels in heart failure. Expert Rev Mol Diagn 2014;4:262; with permission.

ARCHITECT and VIDAS are the frequently used automated assays (using the same antibodies as BGM assay).

BGM developed a galectin-3 ELISA kit and used rat monoclonal antimouse galectin-3 antibody attached to a microtiter plate. The secondary antibody is a traced mouse monoclonal antihuman galectin-3 antibody. The concentration of galectin-3 can be determined with spectrophotometry with the help of another substrate, and at least 30 μL of serum or plasma is required. This assay is not automated, and has a long turnaround time of 3.5 hours; however, it is often used because of its low operating costs, and because it has received US Food and Drug Administration (FDA) approval.[18–20] The R&D ELISA uses the same sandwich ELISA technique as BGM, but requires a sample volume of 50 μl; it is not FDA approved and is mainly used in research settings.[18,21]

A cooperation of BGM and Abbott provided the first automated galectin-3 assay, known as ARCHITECT. The ARCHITECT assay uses the same antibodies as the BGM galectin-3 ELISA kit. In addition, a tracer as well as another substrate is required to run a chemiluminescent immunoassay. Abbott offers 2 different demand-adapted assays and both these assays require a 25-μL sample volume. It has a short turnaround time of only 18 minutes, and therefore can be effective when multiple samples are analyzed on a daily basis.[18,22,23] The VIDAS, produced by bioMérieux, is another automated immunoassay based on a strip system, which can be evaluated using a specific machine. Although this assay requires a high sample volume of 200 μL, it has a short runtime of 20 minutes. VIDAS is consistent with the BGM assay; however, it has higher running costs.[18,24]

In order to interpret the information conferred by changes in biomarker levels over time, it is of crucial importance to understand parameters of variation. A recent study investigated the variation of common and novel biomarkers in 28 healthy controls and 83 patients with HF. Galectin-3 was found to be a stable biomarker with very low variability. The intraindividual coefficient of variation (CVi) was reported, as well as the reference change value (RCV), which is a marker of percentage of change that indicates a relevant change. Galectin-3 had low indices of variation: a CVi of 8.1% and an RCV of 25.0%, which is lower than, for example, NT-proBNP (CVi, 16.6% and RCV, 64.3%).[25] A low CVi of galectin-3 (short-term, 4.5%; long-term, 5.5%) was also shown in 20 healthy controls and 59 patients with HF.[26]

GALECTIN-3 LEVELS: TRENDS IN HEALTHY INDIVIDUALS

Galectin-3 reference intervals in healthy individuals have been derived from large cohort studies, such as the prevention of renal and vascular end-stage disease (PREVEND) study, Framingham study, and the National FINRISK study. Galectin-3 levels gradually increase with age[23,27] and are also slightly higher in women than in men.[27] Galectin-3 levels also vary depending on race. In a substudy of the Atherosclerosis Risk in Communities (ARIC) study, galectin-3 levels were evaluated in 1809 subjects; although baseline levels were higher in healthy black individuals compared with healthy white individuals, galectin-3 did not strongly predict HF and death in black people. However, galectin-3 levels were independently associated with HF or death as a composite end point and also provided improved discrimination in Harrel's C statistic in white subjects.[28]

NEW-ONSET HEART FAILURE

New-onset HF may present as acutely decompensated HF (ADHF; eg, after acute MI) or may start subacutely, which makes the diagnosis of the condition more difficult; for example, in dilated cardiomyopathy.[12] The following studies highlight the use of galectin-3 as a biomarker in predicting new-onset HF in the general population.

In the Framingham Offspring Cohort, which included 3353 participants (initially N = 3450), galectin-3 was significantly associated with an increased risk for new-onset HF and all-cause mortality after adjustment for BNP and several other clinical variables.[29] The Rancho Bernardo Study was an outcome analysis of 1389 subjects from the general elderly population with a mean age of 70 years. Increased galectin-3 was a proportional predictor of cardiovascular death and all-cause mortality, also after adjustment for NT-proBNP, in subjects without previously diagnosed cardiovascular disease.[30] However, this study did not evaluate new-onset HF.

The FINRISK cohort (N = 8444) study showed that increased galectin-3 levels were proportional to an increased risk of cardiovascular events in the general population. However, there was no significant relationship in predicting HF incidence after adjusting for NT-proBNP.[31] In addition, in the PREVEND cohort study (N = 5958), which evaluated the usefulness of serial galectin-3 measurements in the general population, a persistently increased galectin-3 level independently showed an increased risk of developing new-onset HF.[32]

A recently published meta-analysis including 18 studies with 32,350 subjects showed an increased risk of all-cause mortality, cardiovascular mortality, as well as HF in individuals with increased galectin-3 levels.[1] The utility of galectin-3 levels to predict all-cause mortality and new-onset HF in the general population is summarized in Table 2.

PROGNOSIS AND RISK STRATIFICATION: ACUTE HEART FAILURE

Acute HF (AHF) is characterized by a sudden onset of HF symptoms, usually also combined with signs of HF.[12] AHF can be a new-onset HF, or, more commonly, a decompensation of preexisting HF (chronic HF [CHF]), and can be caused by intrinsic or extrinsic factors, which are described elsewhere.[12] AHF is the leading cause of hospitalization in elderly people in Europe, and is a major contributor to overall health care cost as well as mortality.[33]

Although galectin-3 levels are usually increased in patients with AHF, it has a limited role in diagnosing AHF.[34] BNP, a marker of myocardial stretch and overload, is the leading biomarker in diagnosing AHF in patients presenting with dyspnea to the emergency department.[35] Because galectin-3 is a slow marker, reflecting fibrotic processes, it seems to be particularly useful in identifying patients with AHF who are at an increased risk for future events and in selecting those who require a more intensive follow-up. Several studies have been published and reviewed demonstrating the utility of galectin-3 in AHF.[36–41]

In 2010, a subanalysis conducted on 56 patients with ADHF showed a significant relationship between increased galectin-3 levels and increase in 4-year mortality, independent of echocardiographic parameters.[34]

More recently, Mueller and colleagues[35] included 251 subjects with AHF and considered galectin-3 useful in determining the probability of 1-year all-cause mortality; soluble suppressor of tumorgenicity 2 (sST2) and BNP were also equally useful in predicting this end point. Another study, including 101 patients, showed a significant improvement in predicting the likelihood of a 60-day readmission in patients with ADHF if galectin-3 was evaluated together with BNP. When used as a sole marker, galectin-3 also

Table 2
Galectin-3 in the general population

Study or Author Name, Date	Sample Size (N)	Assay	Median Gal-3 Levels (ng/mL)	Follow-up Period (y)	End Points	Main Findings/ Results
Framingham Offspring Cohort,[29] 2012	3353	BGM	Women, 14.3 Men, 13.1	8.1	Several sequences of events	Galectin-3 significantly predicted new-onset HF after adjustment for BNP and several other clinical variables in general population
FINRISK cohort,[31] 2015	8444	ARCHITECT Galectin-3	Women, 12.0 Men, 11.5	15	All-cause mortality Cardiac death MI Ischemic stroke HF	Predictor for incident HF and death after correction for NT-proBNP in general population
PREVEND study,[78] 2016	5958	BGM	Baseline, 10.7; after ~9 y, 11.5	Median 9.3	New-onset HF CV death All-cause mortality New-onset atrial fibrillation CV event	Increases in galectin-3 associated with increased blood pressure and urinary albumin >30 mg/24 h

Abbreviations: BGM, BG Medicine; BNP, B-type natriuretic peptide; CV, cardiovascular; Gal-3, galectin-3; HF, heart failure; MI, myocardial infarction; NT-proBNP, N-terminal proBNP.

showed significant prognostic value in predicting 60-day readmission in patients with ADHF with preserved ejection fraction (area under the curve, 0.85; $P<.001$).[42] Likewise, the GALectin-3 in Acute heart failure (GALA) study, which used a small study group of 115 patients, compared the values of galectin-3, NT-proBNP, and cardiac troponin I (cTnI) in predicting 30-day all-cause mortality and 1-year mortality (among other end points) and concluded that galectin-3 (but not NT-proBNP) was useful in predicting the 30-day all-cause mortality after hospital admission for AHF. The study also showed that although galectin-3 had no prognostic utility in predicting 1-year mortality, NT-proBNP had a significant predictive value; In contrast, cTnI could predict neither the 30-day nor the 1-year mortality.[43]

All the studies mentioned earlier are also in line with a pooled analysis of 902 patients hospitalized with AHF, which showed that when plasma galectin-3 levels exceeded 17.8 ng/mL, the risk for readmission (at 30, 60, 90, or 120 days) and death were significantly increased, also after adjustment for common variables, including BNP (**Fig. 2**, **Table 3**).[44] Galectin-3 very strongly reclassified patients from low-risk to high-risk categories, and vice versa; that is, patients who were classified as having high risk in fact had low risk for death and/or hospitalization. In a subsequent study, low galectin-3 levels in patients with AHF proved to be potentially effective in identifying those who could be (safely) discharged. In 592 patients in the Coordinating Study Evaluating Outcomes of Advising and Counselling in Heart Failure (COACH), galectin-3 was an effective marker in predicting the absolute absence of events within 180 days from the time of discharge after an episode of ADHF. Galectin-3 showed a

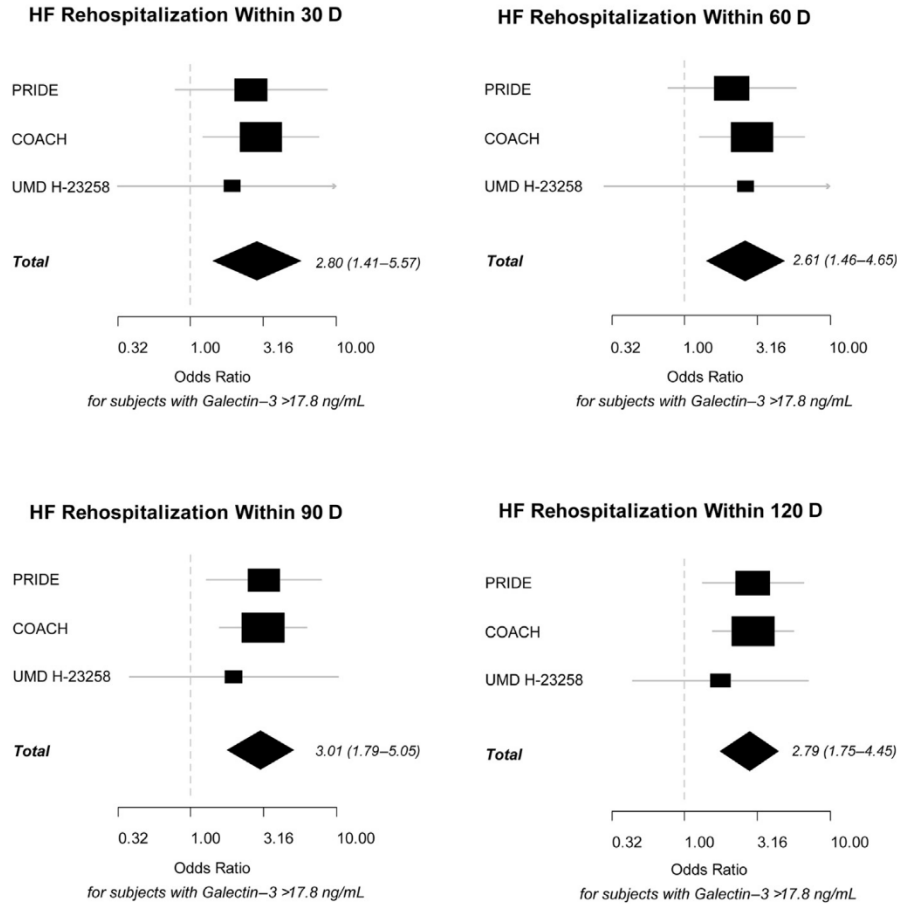

Fig. 2. Meijers pooled analysis. The odds ratio of HF rehospitalization at different time points across 3 different studies (N-terminal pro- BNP Investigation of Dyspnea in the Emergency Department [PRIDE], Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure [COACH], and University of Maryland [UMD] Pro-BNP for Diagnosis and Prognosis in Patients Presenting with Dyspnea study H-23258). (*From* Meijers WC, Januzzi JL, defilippi C, et al. Elevated plasma galectin-3 is associated with near-term rehospitalization in heart failure: a pooled analysis of 3 clinical trials. Am Heart J 2014;167(6):856; with permission.)

Table 3
Galectin-3 in acute heart failure studies

Study or Author Name, Date	Sample Size (N)	Assay	Median Gal-3 Levels (ng/mL)	Follow-up Period	End Points	Main Findings/Results
Subset of PRIDE study,[34] 2010	56	BGM	15	4 y	Mortality	Increased Gal-3 associated with increase in 4-y mortality, independent of echocardiographic results
Mueller et al,[35] 2016	251	ARCHITECT	22	1 y	All-cause mortality	Predictor of 1-y all-cause mortality Not useful for diagnosis of acute HF in contrast with BNP
Sudharshan et al,[42] 2017	101	BGM/Abbott Gal-3 assay	Not readmitted after 60 d 21.0/24.6 Readmitted 60 d 27.2/32.6	60 d	30-d and 60-d hospital readmission	Predicting 60-d (not 30-d) readmission in patients with HFpEF (significant without BNP)
GALA study,[43] 2017	115	VIDAS Gal-3	Patient who died, 44 Other, 26	1 y	30-d all-cause mortality	Predictor of mortality 1 mo after hospital admission
Pooled analysis of: COACH PRIDE UMD H-23258,[44] 2014	902	BGM	18.2	≥120 d	All-cause mortality and rehospitalization	Predictor for near-term readmission
COACH,[36] 2015	592	BGM	No event, 18.9 Event: 24.5	180 d	All-cause mortality and/or HF rehospitalization	Predictor of absence of events within 180 d at the time of discharge after an episode of acutely decompensated HF
RELAX-AHF trial,[45] 2017	1161	BGM	Baseline, 21.1 At 180 d, 20.6	180 d	Time to CV mortality	Gal-3: stable over time (baseline to day 60) No benefit of repeated measurements could be proved Gal-3 is not independently associated with CV mortality within 180 d
Boulogne et al,[66] 2017	55 acute HFrEF 20 chronic HFrEF	ARCHITECT	Baseline AHF, 22.8 CHF, 13.0 30 d after discharge	1 y	Death Unplanned admission for CV cause	Gal-3 level was significantly higher in AHF compared with CHF Gal-3 values remained stable in both groups over time

Abbreviations: BGM, BG medicine; BNP, B-type natriuretic peptide; CHF, chronic heart failure; COACH, coordinating study evaluating outcomes of advising and counseling in heart failure; CV, cardiovascular; Gal-3, galectin-3; GALA, GALectin-3 in Acute HF; HF, heart failure; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction; PRIDE, N-terminal pro- BNP investigation of dyspnea in the emergency department; RELAX-AHF, RELAXin acute heart failure (RELAX-AHF); UMD, university of maryland Pro-BNP for Diagnosis and Prognosis in Patients Presenting with Dyspnea study H-23258.

good sensitivity in predicting the absence of events when values were less than 11.8 ng/mL. The results were also validated in the independent TRIple pill vs Usual care Management for Patients with mild-to-moderate Hypertension (TRIUMPH) HF cohort, which included 285 subjects.[36] Galectin-3 may thus be used to direct scarce resources to those patients who truly have an increased risk of having events during follow-up, and steering unnecessary care away from low-risk patients.

In contrast, some other studies showed a limited value of galectin-3 in predicting outcomes in patients with AHF. The RELAXin in Acute Heart Failure (RELAX-AHF) trial compared different biomarkers at multiple times in patients with AHF (n = 1161). Galectin-3 was stable over time (baseline to day 60) and a benefit of repeated measurements could not be proved,[45] whereas high-sensitivity C-reactive protein and sST2 had an improved predictive value on day 14 after hospital admission.[45] This finding was confirmed in a recent study involving 2033 patients with AHF from the ProB- NP Outpatient Tailored Chronic Heart Failure (PROTECT) study; galectin-3 levels remained stable over time and serial measurements offered limited prognostic value in these patients.[46]

In conclusion, plasma galectin-3 seems to be an additional risk marker in the diagnosis and prognosis of AHF. However, it is important to realize that galectin-3 is not a cardiac-specific biomarker and may also reflect other systemic pathophysiologic processes, such as activation of the inflammatory axis on top of cardiovascular disorder.

PROGNOSIS AND RISK STRATIFICATION: CHRONIC HEART FAILURE

After the initial emergency of AHF has resolved, and the condition of HF persists for more than 3 months,[47] the condition is then referred to as CHF. Like AHF, CHF may have different causes, including a diseased myocardium, abnormal loading conditions, and arrhythmias.[12] Compared to healthy individuals, galectin-3 levels are usually increased in patients with CHF (**Table 4**).[25,46,48,49,53,54] The prognostic utility of galectin-3 in CHF was first reported in a study by Lin and colleagues[50] on 106 patients with CHF. Galectin-3 levels also correlated with markers of cardiac remodeling after adjustment for age, gender, and New York Heart Association (NYHA) class. Another study, in 2010, also showed the association between galectin-3 and left ventricular remodeling and indicated that galectin-3 was able to predict long-term all-cause mortality in patients with CHF even after adjusting for age, gender, severity of HF, and renal function.[51]

A role for serial galectin-3 measurements in patients with CHF has also been explored. Serial galectin-3 measurements in the Valsartan Heart Failure Trial (Val-HeFT)[49] were prognostically significant in patients with CHF. Galectin-3 measurements from 1650 patients were included at the baseline, and an elevation of galectin-3 after 4 months (N = 1346) significantly correlated with HF hospitalization, all-cause mortality, and first morbid event after adjusting for NT-proBNP and estimated glomerular filtration rate (eGFR). Furthermore, there was a decrease in HF hospitalization when baseline galectin-3 levels were lower than 16.2 ng/mL.[49]

In a recent study involving patients with CHF from the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) (N = 1329), galectin-3 levels were measured at baseline and at 3 months; the primary composite end point was all-cause mortality or rehospitalization. Serial galectin-3 measurements were also useful in this study: a 15% increase over 3 to 6 months is associated with a 50% increase in death and HF rehospitalization.[52]

In contrast, previous studies showed that there was no added value of repeated galectin-3 measurements (at baseline and after 6 months) in patients with CHF.[53] Several other studies support these observations; for instance, in a recent study, serial galectin-3 measurements in 180 patients with CHF with reduced ejection fraction (EF) over 2 years did not have any significant prognostic value in predicting risk of death or cardiac transplant after adjusting for clinical variables, BNP, and cTnT.[54]

Galectin-3 levels in CHF also seem to vary depending on other factors, such as rehabilitation or comorbidities. Cardiac rehabilitation seems to reduce galectin-3 levels in patients with CHF. A recent study showed that there was a 6.3% median decrease of galectin-3 and other cardiac biomarkers, such as sST2 and midregional pro–atrial natriuretic peptide (proANP), in patients with CHF and reduced EF (ie, EF $\leq$ 45%) following a cardiac rehabilitation.[55] Kidney function seems to play a key role in determining serum galectin-3 values and also influences its predictive value in HF.[56–58] A Danish research group found a relationship between an increased galectin-3 plasma concentration (>16.90 ng/mL) and a reduced eGFR, along with increased levels of proANP, chromogranin A, and copeptin, in a prospective study involving 132 patients with chronic HFrEF.[58] In patients with both HF and reduced renal function, galectin-3 has a decreased predictive value after adjustment for renal function.[56] Another study

Table 4
Galectin-3 in chronic heart failure studies

Study or Author Name, Date	Sample Size (N)	Assay	Median Gal-3 Levels (ng/mL)	Follow-up Period	End Points	Main Findings/Results
Meijers et al,[25] 2017	Healthy controls = 28 CHF = 83	BGM	Controls, 10.7 CHF, 16.1	4 mo and 6 wk Up to 5 y	HF rehospitalization or all-cause mortality	Stable biomarker with very low variability
Substudy of COACH trial,[53] 2011	592	BGM	HFrEF, LVEF $\leq$ 40% = 19.9 HFpEF, LVEF>40% = 20.2	18 mo	Rehospitalization for HF or death	No added value of repeated galectin-3 measurements at baseline and after 6 mo in patients with HF Stronger predictive value in HFpEF Doubling of galectin-3 associated with a hazard ratio of 1.38 for primary end point after correction
Miller et al,[54] 2016	180 (LVEF $\leq$ 40%)	BGM	Baseline, 23.2	2 y	Death/cardiac transplant, HF-related hospitalization	Galectin-3 (>22.1 ng/mL) was predictive of the end points, but only sST2 was an independent predictor
PROTECT trial,[46] 2016	2033	Not standardized	Baseline, 36.3	180 d	30-d all-cause mortality, 30-d death or rehospitalization for renal/CV causes 180-d all-cause mortality	Stable concentration in patients with CHF who were hospitalized for AHF
Valsartan Heart Failure Trial,[49] 2013	1650	BGM	Baseline Average, 16.2 Patients who died, 18.3 Survivors, 15.8	Median, 23 mo	Mortality, first morbid event, hospitalization for HF	Increase in galectin-3 values over time was an independent predictor of worse outcome Valsartan in patients with low galectin-3 level was associated with a reduced rate of hospitalization for HF

(*continued on next page*)

Table 4
(continued)

Study or Author Name, Date	Sample Size (N)	Assay	Median Gal-3 Levels (ng/mL)	Follow-up Period	End Points	Main Findings/Results
Billebeau et al,[55] 2017	107 LVEF $\leq$ 45%	ARCHITECT	Baseline, 18.4 After CR, 17.5 No change in no-CR group (P = .595)	4–6 mo	—	Significant (P<.0001) decrease after CR
Stoltze Gaborit et al,[58] 2016	132 HFrEF	BGM	Baseline, 16.9	Cross-sectional study without follow-up	—	>16.90 ng/mL was related to a reduced eGFR and increased proANP, chromogranin A, and copeptin Galectin-3 values were not associated with echocardiographic parameters
Zamora et al,[56] 2014	876	VIDAS	12.3 for eGFR $\geq$ 60 mL/min/1.73 m^2 16.1 for eGFR 30 to <60 mL/min/1.73 m^2 24.5 for eGFR <30 mL/min/1.73 m^2	Mean, 4.2 y	All-cause mortality, CV mortality, HF hospitalization	Limited value (not significant) in HF prognosis for all-cause and CV mortality after adjustment for renal function
Imran et al,[1] 2017	32,350 Meta-analysis of 18 studies, general population and patients with HF	Most commonly BGM ARCHITECT	—	Median, 5 y	CV mortality, all-cause mortality, HF	Increased values are a predictor for all-cause mortality, CV mortality, and HF
HF-ACTION trial,[59] 2014	813	BGM	Baseline, 13.9	2.5 y	All-cause mortality and all-cause hospitalization	Contributed to net risk classification of SCD when added to NT-proBNP measurements

Abbreviations: AHF, acute heartfailure; BGM, BG medicine; BNP, B-type natriuretic peptide; CHF, chronic heart failure; COACH, coordinating study evaluating outcomes of advising and counseling in heart failure; CR, cardiac rehabilitation; CV, cardiovascular; eGFR, estimated glomerular filtration rate; Gal-3, galectin-3; HF, heart failure; HF-ACTION trial, HF- a controlled trial investigating outcomes of exercise training; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro- BNP; pro-ANP, pro–atrial natriuretic peptide; SCD, sudden cardiac death; sST2, soluble suppressor of tumorgenicity 2.

involving 876 patients also showed limited value in HF prognosis when adjusted for renal function.[56]

Galectin-3 seems to add prognostic information on top of existing HF biomarkers in patients with CHF; galectin-3 and ST2 significantly contributed to net risk classification of sudden cardiac death (SCD) but not pump failure when added to NT-proBNP measurements in 813 subjects with CHF from the HF- A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION); In contrast, NT-proBNP was a very strong predictor of deaths caused by pump failure.[59] Certain studies also indicated that the biomarker sST2 could be superior to galectin-3 in risk stratification of patients with CHF.[60] A recent study compared the utility of serial sST2 measurements with galectin-3 measurements in ambulatory patients with CHF and concluded that, in multivariable models adjusted for BNP, cTnT, and clinical variables, serial galectin-3 measurements did not reclassify patients into higher risk groups, whereas serial measurement of sST2 offered additional prognostic value in predicting death or cardiac transplant in patients with CHF.[54]

In addition, a published meta-analysis in 2017[1] showed a significant increase of cardiovascular disease mortality risk for every standard deviation increase of galectin-3 in patients with HF (hazard ratio, 1.44 [1.09–1.79]). Galectin-3 could thus provide additional prognostic value compared with that provided by conventional cardiovascular disease risk factors.

GALECTIN-3 AND HEART FAILURE WITH PRESERVED EJECTION FRACTION

Preventive medicine is becoming a major focus in modern therapy guidelines. A major part of the population more than 65 years of age is diagnosed with arterial hypertension, which can potentially lead to HFpEF. Individuals who are at a higher risk of developing HFpEF need to be identified, and galectin-3 can be an effective biomarker in early detection of HFpEF. Most of the articles were published before the release of the 2016 ESC HF guidelines,[12] and patients currently classified as having HFmrEF were included in the HFpEF category. The previous terminology with an EF cutoff of 50% is used here.

HFpEF can be diagnosed when a combination of clinical symptoms and signs, an EF more than 50%, and specific echocardiographic criteria are present. Echocardiography commonly shows either a structural heart disease (left atrial enlargement, left ventricular hypertrophy) or diastolic dysfunction, or both in patients with HFpEF.[12] Plasma galectin-3 levels tend to be similar in patients with HFpEF and HFrEF; however, studies show that galectin-3 values can directly relate to the severity of diastolic dysfunction.[61] A smaller study (N = 63 patients) also found a positive association between the serum galectin-3 levels and left ventricular diastolic filling properties, which was determined by late gadolinium-enhanced cardiac magnetic resonance imaging.[62] In the ALDOsterone Heart Failure (ALDO-DHF) study, increased galectin-3 plasma values directly correlated with cardiac function in patients with HFpEF. When galectin-3 level was more than 12.1 ng/mL at baseline, echocardiography revealed an enlarged left atrium and diastolic dysfunction (increased E/E′ ratio). However, there was no significant correlation of galectin-3 plasma values (N = 377) and spironolactone treatment in patients in the Aldo-DHF trial.[63] Because low values of NT-proBNP do not exclude HFpEF diagnosis, increased galectin-3 level can raise the suspicion of HFpEF and galectin-3 could therefore have a diagnostic utility in patients with HFpEF.[53,64]

Galectin-3 can also be used in prognosticating patients with HFpEF; galectin-3 was found to be the most accurate risk predictor of adverse events within 5 years in patients with HFpEF. A total of 1385 patients with HF were included in the study; 106 patients had a preserved ejection fraction.[65] These data support the results from the substudy of the COACH trial. The substudy (N initially 592, N = 114 with HFpEF), with a follow-up period of about 1.5 years, showed a higher predictive value of galectin-3 in HFpEF (EF>40%) for rehospitalization and death compared with HFrEF.[53]

GALECTIN-3 LEVELS IN SYSTEMIC DISORDERS

Although galectin-3 is used as a biomarker in HF, it seems to be neither a cardiac-specific biomarker nor a cardiac-specific protein. Variations of galectin-3 plasma levels depend on comorbidities, as shown in **Fig. 3**. Healthy individuals have the lowest baseline galectin-3 levels[25]; although galectin-3 levels increase in CHF[66] and ADHF,[34] the highest increases are observed in patients with end-stage kidney disease.[57] Increased galectin-3 levels are also observed in pulmonary conditions such as pneumonia and chronic obstructive pulmonary disease.[69,67] Very high galectin-3 levels are observed in sepsis.[68,69]

In otherwise healthy patients with HF, the FDA approved a plasma galectin-3 cutoff value of 17.8 ng/mL.[65] Correcting galectin-3 values for comorbidities/covariates or different circumstances is complex and clinicians have yet to understand the specific covariates. Although the predictive value of

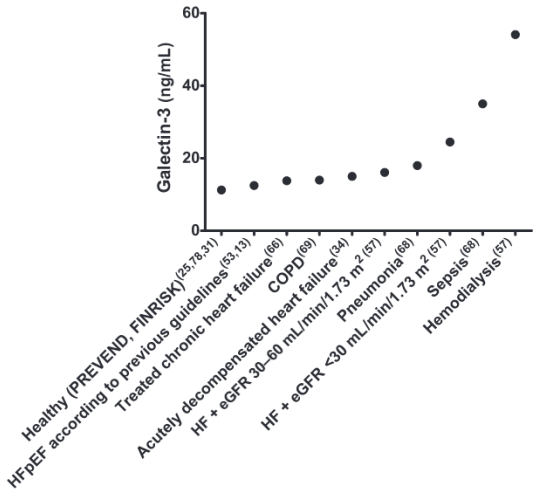

Fig. 3. Variation of galectin-3 levels in systemic diseases and in the general population. COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate.

galectin-3 in patients with HF diminishes significantly after adjustment for renal function,[56] increased galectin-3 levels in patients with severe renal insufficiency independently predicted cardiovascular end points, infections, as well as all-cause mortality.[57] A minimal influence of diabetes mellitus on the predictive power of certain HF biomarkers, such as galectin-3, NT-proBNP, and hs-TNT, was found.[70] Diabetes was shown to influence the predictive value of ST2, because increased ST2 values were associated with an increased risk of HF in nondiabetic patients.[70]

RELATION BETWEEN SERUM GALECTIN-3 AND MYOCARDIAL GALECTIN-3 EXPRESSION

There are contradicting results concerning the direct relationship of plasma galectin-3 levels, myocardial galectin-3 expression, and myocardial fibrosis.

The relationship between plasma and myocardial galectin-3 values was evaluated in a canine model, which showed a direct relationship in a model of pressure overload.[61] An in vitro cell model also visualized an increase in galectin-3 level following stretch of cardiomyocytes,[61] suggesting that the heart can also be a source of this protein.

In a study involving 150 participants, a direct relationship between increased plasma galectin-3 (>14.6 ng/mL) and the amount of myocardial fibrosis could also be detected when imaging was done with contrast-enhanced cardiac MRI in patients with nonischemic dilated cardiomyopathy.[71]

Correlation of plasma and myocardial galectin-3 as a marker in nonischemic, noninflammatory dilated cardiomyopathy (N = 40) versus inflammatory cardiomyopathy (N = 77) and its predictive capability in fibrosis was investigated recently. Galectin-3 levels in the plasma correlated neither with endomyocardial levels of galectin-3 nor with cardiac fibrosis in left ventricular biopsies of patients with the aforementioned types of cardiomyopathy. In the same patients, left ventricular biopsies revealed a direct correlation between myocardial galectin-3 expression and fibrosis.[72]

GALECTIN-3 AS A BIOTARGET

New research has highlighted the potential of modulating the development of cardiac fibrosis by blocking profibrotic proteins. Galectin-3 has been shown to be a specific modulator of different inflammatory and profibrotic processes in humans; clinical trials on galectin-3 inhibitors in different disease settings are currently ongoing, and these include several fibrotic disorders (eg, hepatic, renal, and pulmonary fibrosis) as well as malignancies (eg, colorectal cancer), as summarized in **Table 5**.

The upregulation of galectin-3 in rats prone to HF was shown to be strongly associated with decompensated HF.[17] Galectin-3 colocalized with macrophages, and upregulation of galectin-3 was the result of macrophage activation in heart tissue.[17] In another study, injecting galectin-3 into the pericardial sac of rats also triggered fibrosis and resulted in significant cardiac dysfunction.[73] Although usually associated with macrophages, a recent in vitro study also found galectin-3–expressing cultured cardiomyocytes after activation by protein kinase C.[74] Furthermore, galectin-3 knockout mice were resistant to angiotensin II–induced pressure overload and did not develop myocardial fibrosis and left ventricular dysfunction, compared with wild-type C57BL/6J mice, and this showed that galectin-3 was a culprit protein in cardiac fibrosis and HF.[75,76]

Different carbohydrate-based ligands of galectin-3, such as *N*-acetyllactosamine and modified citrus pectin (MCP), were studied in the setting of myocardial dysfunction. Treatment with *N*-acetyllactosamine, which binds to the CRD of galectin-3, decreased cardiac fibrosis, preserved the fractional shortening, reduced left ventricular end-diastolic pressure, reduced lung weight, and improved survival in HF-prone rats.[75] MCP, another galectin-3 inhibitor (as well as spironolactone), prevented cardiac dysfunction and hypertrophy, inhibited collagen type I synthesis, and decreased myocardial as well as renal collagen deposition in aldosterone-treated rats.[77] In addition, TD-139 a thiodigalactoside analogue, was studied in a phase IIa trial for the treatment

Table 5
Overview of galectin-3 inhibitors

Gal-3 Inhibitor	Mechanism of Action	Disease	Studies Trials
TD139	High-affinity inhibitor Binds to CBD Blocks TGF-β–induced β-catenin activation Diminishes lung fibrosis	Pulmonary fibrosis	Clinical phase II completed (NCT02257177)[67]
GR-MD-02	Proprietary galactoarabinorhamnogalacturonan polysaccharide polymer Binds to CBD	Nonalcoholic steatosis hepatis/liver fibrosis	Murine model (higher potency than GM-CT-01 in treating liver fibrosis)[79] Clinical phase II[80] (NCT02421094)
	—	Psoriasis	Clinical phase II (NCT02407041)
	—	Metastatic melanoma Melanoma I	Clinical phase I (NCT02407041)
MCP /GCS 100	Polyvalent glycan inhibitor MCP-derived polysaccharide Binds to CBD Reversion of fibrosis, inhibition of cell migration, induction of apoptosis	NASH	IIb discontinued (La Jolla Pharmaceutical)
		Chronic kidney disease caused by diabetes	Clinical phase II (NCT02312050)
	—	Chronic lymphocytic leukemia[81]	Clinical phase II completed (NCT00514696)
	—	Diffuse large B-cell lymphoma[82]	Clinical phase I/II withdrawn (NCT00776802)
	—	Multiple myeloma[83]	Phase I (NCT00609817)
	—	Vascular fibrosis	Rat[84]
		Breast cancer	In vitro[85]
		Hypertension	Clinical study (NCT01960946)
		Prostate cancer	In vitro[85,86] Clinical phase III (recruiting) (NCT01681823)
		Osteoarthritis	Clinical phase III (NCT02800629)
		Ovarian cancer	In vitro[87]
		Renal cell carcinoma	In vitro[88]
		Chronic kidney disease	Clinical phase II (NCT02333955)
		Hypertension, acute kidney injury	In vitro[89]
		Liver metastasis of colon cancer	Mouse[90]

(*continued on next page*)

Table 5
(*continued*)

Gal-3 Inhibitor	Mechanism of Action	Disease	Studies Trials
N-acetyllactosamine	Attenuation of fibrosis	Cardiac fibrosis	Rat[75]
Lactulose L-leucine	Binds to CBD Inhibition of metastasis	Prostate cancer metastasis	Mouse[91]
Galectin-3C	Binds to CBD Inhibits tumor growth Reduces metastasis and tumor size	Multiple myeloma Breast cancer metastasis	Mouse[92] Mouse[93]
Td131_1	Binds to CBD Activation of apoptosis in tumor cells	Papillary thyroid cancer	In vitro[94]
N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP)	Prevention of cardiac fibrosis	Cardiac fibrosis	Rat[73]
Chemically modified, nonanticoagulant heparin derivatives	Binds to CBD Attenuation of galectin-3–mediated metastasis	Pulmonary metastasis of colon cancer and human melanoma	Mouse[95]
RN1	Binds to CBD	Pancreatic ductal adenocarcinoma	Mouse xenograft model[96]

Abbreviations: CBD, carbohydrate binding domain; MCP, modified citrus pectin; NASH, nonalcoholic steatohepatitis; TGF, transforming growth factor.
Adapted from de Boer RA, van der Velde AR, Mueller C, et al. Galectin-3: a modifiable risk factor in heart failure. Cardiovasc Drugs Ther 2014;28:243; with permission.

of idiopathic pulmonary fibrosis in the form of an inhaled powder (NCT02257177). Currently a phase IIb trial is being designed. Because this compound is not systemically available, its effects on (preventing) cardiac fibrosis have not been tested.

New systemically available galectin-3–specific inhibitors need to be developed and investigated. The possibilities are intriguing if a galectin-3 inhibitor with high affinity and a preventive effect on the development of HF were to be discovered. This breakthrough could be an opportunity to further reduce HF hospitalization, especially in patients with high galectin-3 levels, who, although treated with angiotensin II receptor blockers (valsartan),[49] did not show a reduced risk of hospitalization.

SUMMARY

In the last decades, galectin-3 has been intensely studied, and its role in various cellular and extracellular functions has been established. More recently, a role for galectin-3 in cardiac tissue remodeling has been explored. Specifically, galectin-3 plays a dominant role in cardiac inflammation, and fibrosis. Because galectin-3 is secreted into the systemic circulation, its levels can be measured, and its role as a biomarker was investigated in numerous studies in healthy subjects, in the elderly, and in patients with coronary artery disease, hypertension, renal disease, and HF. In a recent meta-analysis, galectin-3 was validated as a biomarker with independent prognostic value for mortality and HF rehospitalization. Currently clinicians lack tools acting on the increased risk conferred by galectin-3 (or any other biomarker), the clinical importance is minor. More promising, therefore in animal models, (genetic) deficiency of galectin-3 results in abolishment of tissue fibrosis, which was confirmed in numerous studies of renal, liver, lung, and cardiac fibrosis. Studies with oral inhibitors recapitulated this, and therefore the most promising outlook for galectin-3 is as an amenable target for tissue fibrosis. Several trials are underway with the aim of validating this concept; if proven useful, the authors predict it will have a major impact on the treatment of several multifactorial diseases.

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