

Galectin-3: A Novel Blood Test for the Evaluation and Management of Patients With Heart Failure

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Replacement of functional myocytes with crosslinked collagen as a result of tissue fibrosis is a final common pathway that is central to the progression of heart failure (HF), irrespective of etiology. In response to a variety of mechanical and neurohormonal stimuli, macrophages secrete galectin-3, which works as a paracrine and endocrine factor to stimulate additional macrophages, pericytes, myofibroblasts, and fibroblasts. The response to this signal is cellular proliferation and secretion of procollagen I. This protein is then irreversibly crosslinked to form collagen and result in cardiac fibrosis. With a commercially available assay, galectin-3 can now be measured in blood and has been found to aid in the prognosis of both systolic and nonsystolic HF. Measurement of galectin-3 before hospital discharge, on outpatient evaluation for suspected HF, and approximately twice per year for those with stable symptoms is supported by the evidence available at this time. Levels > 25.9 ng/mL, independent of symptoms, clinical findings, and other laboratory measures, predict a patient who is likely to have rapid progression of HF, resulting in hospitalization and death. In addition, a doubling in galectin-3 level over the course of 6 months, irrespective of baseline value, identifies a high-risk patient in whom additional care management efforts and advanced therapies could be warranted.
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The definition of congestive heart failure (HF) has evolved over the history of medicine. Older conceptualizations placed congestive HF as synonymous with pump failure. In 1933, Lewis described HF as a condition in which the “heart fails to discharge its contents adequately.”¹ However, recent

advances have broadened this considerably to include patients with systolic as well as diastolic dysfunction.²⁻⁴ Experts now define HF as a complex mechanical and neurohumoral syndrome manifested by hemodynamic congestion presenting with dyspnea, orthopnea, paroxysmal nocturnal dyspnea, or peripheral edema, coupled with objective evidence of cardiac dysfunction.^{5,6} It is appreciated that the neurohormonal syndrome leads to changes in myocardial tissue characterized by progressive and marked increases in the presence of fibrosis.⁷

Epidemiology

Congestive HF is a leading cause of emergency room visits, hospitalizations, and death in developed countries.⁶ In 2006, HF-associated health care costs in the United States totaled nearly \$30 billion.³ There are approximately 5 million people in the United States with a diagnosis of HF, with another 500,000 diagnosed each year, causing the expected prevalence to double by the year 2040.⁸

The direct relationship between advancing age and incidence of HF is well established. The incidence of HF nearly doubles for patients > 85 years compared with those < 75 years.⁹ Age contributes to all forms of HF because it is a major determinant of tissue fibrosis and vascular stiffness, which are central to cardiovascular senescence. Hypertension appears to accelerate this aging process in the myocardium and the vasculature.¹⁰

The majority of patients (~ 70%) with HF have underlying coronary artery disease¹¹ and are considered to have ischemic cardiomyopathy with zones of cardiac fibrosis as a result of ischemia and infarction.¹² The extent of coronary artery disease is independently associated with higher mortality, and patients with single-vessel

disease and no history of myocardial infarction (MI) or revascularization should be classified as nonischemic for prognostic purposes.¹³

The epidemiology of nonischemic cardiomyopathy, which includes the remaining one-third of individuals with reduced left ventricular ejection fraction (LVEF) and clinical HF, has a less striking relationship with age; however, it is associated with antecedent hypertension in a majority of cases. Most forms of nonischemic cardiomyopathy have an underlying at-risk substrate, such as a genetic susceptibility, followed by a superimposed myocardial insult, such as myocarditis, alcohol consumption, cardiotoxic medication (anthracyclines), infiltrative diseases (sarcoid, amyloid), radiation, or autoimmune injury. The important aspect of nonischemic cardiomyopathy epidemiology is that, among those discovered to have idiopathic dilated cardiomyopathy, approximately 20% of first-degree family members will be found to have depressed LVEF, which is often asymptomatic and amenable to therapy to prevent worsening.¹⁴ Most forms of nonischemic cardiomyopathy, as the final histopathological process, have excess deposition of collagen in the extracellular matrix (ECM) and tissue fibrosis present at necropsy.¹⁵

There are dissimilarities in progression and survival in HF populations based on HF etiology (ischemic vs nonischemic) and (systolic vs diastolic) pathophysiology.¹⁶ Patients with angiographically diagnosed ischemic HF fare worse than their HF counterparts with nonischemic causes.⁷ Data from a large registry of patients admitted with HF demonstrate that patients with "ischemia/acute coronary syndromes" as a precipitant of HF had approximately 50% excess mortality within the first 90 days following hospital discharge

compared with those with nonischemic HF independent of other risk factors.¹⁷ Once a patient with HF (systolic or nonsystolic) has been admitted with an acute ischemic event, recurrent ischemia remains the dominant reason for readmission in the future.¹⁸ Patients with systolic HF are most likely to present with an inpatient admission for dyspnea, whereas those with diastolic HF are diagnosed and managed primarily on an outpatient basis. Both forms have similar survival rates over time.¹⁹ It appears that all persons with HF have prognosis tied to some extent to the degree of underlying cardiac fibrosis. Thus, new insights into this process of cardiac fibrosis have yielded a breakthrough in understanding the natural history of this disease.

Pathophysiology of Myocardial Fibrosis and Galectin-3

The pathophysiology of HF is directly related to the concept of cardiac remodeling. Increased stress or injury to the myocardium due to uncontrolled hypertension, diabetes mellitus, ongoing ischemia, or acute MI, and other forms of myocyte damage can contribute to cardiac remodeling.¹⁴ Cardiomyocyte adaptations are critical in the remodeling process and include myocyte hypertrophy, reductions in the activation of actin-myosin complexes, a multitude of changes in gene expression, and ultimately, dysfunction on a cellular level. Responses to acute and chronic damage can involve recruitment of immune cells to the myocardium; production of cell signaling proteins from local pericytes, mast cells, and macrophages, resulting in activation of resident fibroblasts and myofibroblasts; and in the final common pathway, the deposition of procollagen into the ECM, which is irreversibly crosslinked to collagen-generating cardiac fibrosis (Figure 1).²⁰

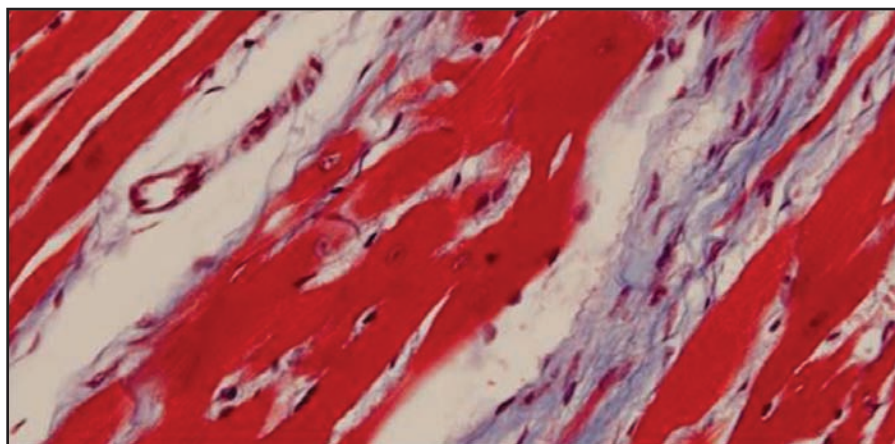
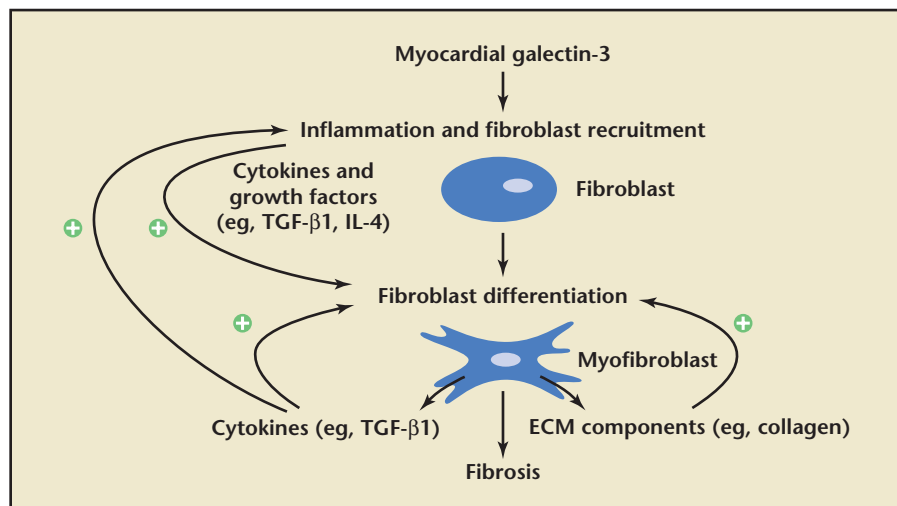


Figure 1. Myocardial galectin-3 levels determined by neurohormonal and mechanical factors direct the activation of fibroblasts and result in cell proliferation and interstitial fibrosis. ECM, extracellular matrix; IL, interleukin; TGF, transforming growth factor.

There are a multitude of regulators involved in the pathophysiology of cardiac fibrosis. The galectin classes of carbohydrate-binding proteins are important participants in this process. Galectins are a large family of carbohydrate-binding proteins involved in the regulation of inflammation, immunity, and cancer.

process. Galectin-3 is the most well-studied galectin subtype and is released by activated macrophages directly in the myocardial extracellular space and blood stream.

Galectin-3 is one of 14 mammalian galectins, is an approximate 30 kDa glycoprotein that has a carbohydrate recognition-binding do-

Galectins are a large family of carbohydrate-binding proteins involved in the regulation of inflammation, immunity, and cancer.

Various subtypes bind to specific carbohydrate molecules, which activate a particular cellular signaling

main of approximately 130 amino acids that enables the binding of β -galactosides.²¹⁻²³ The size of

galectin-3 is reported to measure between 29 and 35 kDa.^{22,23} The size discrepancy is secondary to the broad galectin-3 protein band that is measured with Western blot analysis. Furthermore, a segment of this protein (110-130 amino acids) near the N-terminal domain consists of tandem repeats of short amino acid segments yielding size variability.²⁴ Over the years, the reported size discrepancy of galectin-3 may have created confusion, in that this same protein was described with various synonyms, including Mac-2, carbohydrate-binding protein 35 (CBP-35), IgE-binding protein, RL-29, HL-29, and L-34.²⁵ It is encoded by a single gene, *LGALS3*, located on chromosome 14, locus q21-q22, and is expressed in the nucleus, cytoplasm, mitochondrion, cell surface, and extracellular space.²⁶ Galectin-3 as a paracrine signal is involved in cell adhesion, activation, chemoattraction, growth and differentiation, cell cycle, and apoptosis. Galectin-3 has been demonstrated to be involved in cancer, inflammation and fibrosis, liver disease, renal disease, and various rheumatological conditions.²⁷ In the myocardium, aldosterone is a major stimulus for macrophages to secrete galectin-3, which in turn works as a paracrine signal on fibroblasts to help translate the signal of transforming growth factor- β to increase cell cycle (cyclin D1) and direct both the proliferation of myofibroblasts and the deposition of procollagen 1. In a pivotal paper, Sharma and colleagues²⁸ demonstrated that galectin-3 was the most upregulated protein in an animal model of left ventricular hypertrophy (LVH) and HF. It colocalized with activated myocardial macrophages and had binding sites on cardiac fibroblasts. Recombinant galectin-3 induced cardiac fibroblast proliferation, collagen production, and cyclin D1 expression.

Using placebo control, these investigators demonstrated that intrapericardial infusion of low-dose galectin-3 into healthy Sprague-Dawley rats markedly increased LV collagen density (threefold increase) and reduced LVEF (decreased 22% over 4 weeks). Liu and colleagues²⁹ have confirmed the pathogenetic effects of intrapericardial instillation of galectin-3 in adult male rats. These data strongly suggest that galectin-3 is a critical participant in the pathogenesis and progression of HF.²⁸ Because the tissue secretion of galectin-3 is sufficiently high, it can be detected as a signal in blood, and thus has been developed as a key advance for the clinical assessment of patients at risk for and with established HF.

Galectin-3 in the General Population

In the Prevention of Renal and Vascular End-stage Disease (PREVEND) study,³⁰ galectin-3 levels were measured in 7968 individuals from the general population. Galectin-3 was slightly higher in women than in men and increased from age 30 to 75 years by approximately 1.5 ng/mL. There were significant positive associations found for this protein with age, sex, diabetes, hypertension, hypercholesterolemia, body mass index, and renal function ($P < .001$ for all), and smoking ($P = .002$). These associations were somewhat stronger in women than men. The highest quintile of galectin-3 (median 15.6 ng/mL) incurred a 15% 10-year mortality rate compared with a 5% rate for those in the lowest quartile (median 7.7 ng/mL). Thus, population galectin-3 levels are associated with conventional cardiovascular risk factors, and as a reflection of the chronic vascular damage associated with these conditions, translate into higher all-cause mortality rates at 10 years.

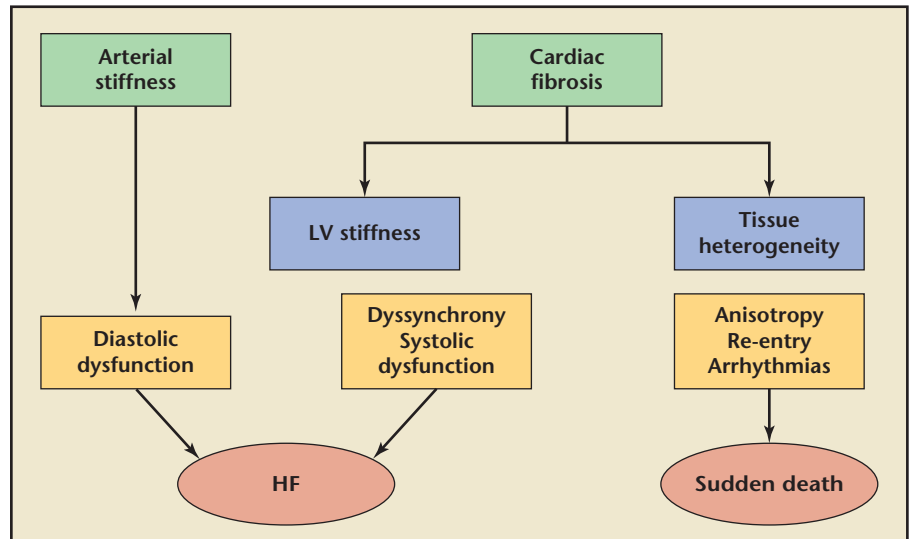


Figure 2. Cardiac fibrosis results in myocardial tissue heterogeneity and vascular stiffness. These processes predispose to arrhythmias and pump failure as the two major manifestations of HF progression. HF, heart failure; LV, left ventricular.

Galectin-3 in Acutely Decompensated HF

Cardiac and vascular fibrosis can lead to the progression of HF by creating tissue heterogeneity and stiffness, resulting in arrhythmias and sudden death or pump failure, as shown in Figure 2. In 2006, van Kimmenade and coworkers³¹ found that galectin-3 levels were elevated in those patients with confirmed HF ($n = 209$) compared with those with other causes of dyspnea ($n = 309$) in the emergency department. Serum galectin-3 was detected with a research-grade enzyme-linked immunosorbent assay (ELISA) kit (BMS279/2; Bender MedSystems, Vienna, Austria) and quantified on a VICTOR2TM plate reader (Perkin Elmer, Turku, Finland). Upon initial blood draw, levels were 9.2 and 6.9 ng/mL for those with and without HF, respectively ($P < .001$). In this study, although both N-terminal pro-B-type natriuretic peptide (NT-proBNP) and galectin-3 were predictive of acute HF ($P < .0001$ for both), the predictive power of NT-proBNP was significantly less than galectin-3 (0.72 vs 0.94 for area

under the receiver operating characteristic curve). In 2008, Milting and coworkers³² found markedly elevated levels of galectin-3 in 55 patients with end-stage HF requiring mechanical support when compared with 40 healthy control subjects.

Galectin-3 in Chronic Stable HF

Approximately one-half of all HF patients will have a galectin-3 level above the upper limit of normal of 17.7 ng/mL.³³ Lin and colleagues³⁴ measured blood galectin-3 in 106 patients with stable HF with a mean age of 61 years, LVEF of 35%, and New York Heart Association (NYHA) functional class of 2.2. Log galectin-3 was significantly correlated with log serum type 3 aminoterminal propeptide of procollagen ($P = .006$), log tissue inhibitor of metalloproteinase-1 ($P = .025$), log metalloproteinase-2 ($P = .016$), and functional class ($P = .034$), but not age, sex, or LVEF. After multivariable adjustment, the relationship between galectin-3 and ECM turnover biomarkers remained significant. These data suggest that galectin-3, as shown in animals, is

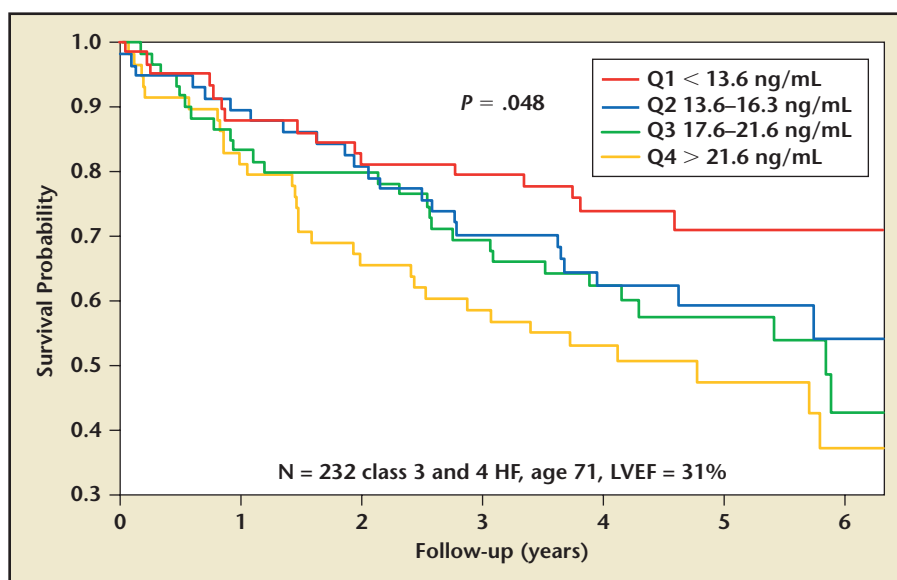


Figure 3. Six-month survival in a cohort of patients with class 3 and 4 low systolic HF according to baseline galectin-3 levels in the DEAL-HF study. DEAL-HF, Deventer-Alkmaar Heart Failure; HF, heart failure; LVEF, left ventricular ejection fraction. Reprinted with permission from Lok et al.³³

actively involved in ECM turnover and fibrosis in humans. In this study, the mineralocorticoid receptor antagonist spironolactone was associated with lower measures of protein turnover. In the Deventer-Alkmaar Heart Failure study (DEAL-HF), Lok and colleagues³³ demonstrated galectin-3 measured by a novel and optimized ELISA kit (BGM Galectin-3TM Assay, BG Medicine, Waltham, MA) and measured on a BioTek ELx800 microplate reader (Biotek Instruments, Winooski, VT), was elevated in chronic HF with a mean concentration of 18.6 ± 7.8 ng/mL, which was 5% elevated above the 17.7 ng/mL cutpoint for normal control subjects. In this study, baseline galectin-3 predicted short-term survival, as shown in Figure 3.

Galectin-3 and the Progression of HF

Unfortunately, few patients have a reversal of HF and return to a normal expected lifespan. Over 90% of patients with HF have a death that is either attributable to pump failure or arrhythmias.⁹ Along the progression to death,

most HF cases are chronicled by frequent hospitalizations and considerable costs to the patients, payers, and societies; thus, tools that aid in the prognosis of HF are inherently management tools as physicians deal with patients and their families in the circumstances nearing the end of life. Because progressive cardiac fibrosis is believed to be a central aspect in the progression of both systolic and diastolic dysfunction as well as the primary substrate for lethal arrhythmias, it is intuitive that a blood marker of cardiac fibrosis would be independently associated with HF hospitalization and death. Listed in Table 1 are the clinical studies of galectin-3 which demonstrate the consistent and graded relationship between galectin-3 levels and the future risk of HF hospitalization and/or death. In the Pro-BNP Investigation of Dyspnea in the Emergency Department (PRIDE) study,³¹ among those patients acutely short of breath in the emergency department, log galectin-3 had an odds ratio of 10.3 ($P = .007$) and 14.3 ($P < .001$) for death and the combination of death or hospitalization, respectively. Galectin-3

had a more than fourfold greater association with these outcomes than other traditional variables including age, NT-proBNP, renal function, and NYHA class.

Serial Measurement

De Boer and colleagues measured galectin-3 in 592 participants of the Counseling in Heart Failure (COACH) trial of disease management.³⁵ Levels of galectin-3 were measured prior to discharge from the hospital and then again at approximately 6-month follow-up. Although levels were stable over this period, the baseline level as well as a doubling of galectin-3 from baseline were independent predictors of HF rehospitalization and death after adjustment for age, sex, and natriuretic peptide levels and other adjusted hazard ratios of 3.34 (95% confidence interval [CI], 2.23-5.01; $P < .001$, baseline fourth quartile) and 1.77 (95% CI, 1.42-2.20; $P < .001$ doubling from baseline), respectively. In this study, galectin-3 had prognostic value in both systolic and nonsystolic HF. In addition, as patients from the first to the fourth quartile were analyzed for the primary outcome, it was observed that in the first quartile there were more rehospitalizations than deaths and in a graded fashion progressing to the fourth quartile, in which the number of deaths exceeded the number of hospitalizations over the 18-month follow-up period (Figure 4).

Multimarker Assessment of HF: Galectin-3, Troponin, and Natriuretic Peptides

In the past decade, assays for BNP and NT-proBNP have revolutionized the evaluation of cardiac dysfunction and HF.³⁶ Natriuretic peptides are released by the myocardium in response to myocardial stretch and other nonmechanical factors, and greatly aid in the diagnosis, prognosis, and management of

Table 1
Summary of Clinical Studies Measuring Galectin-3 in Heart Failure

Study	Sample Size	Study Setting	Galectin-3 Level (ng/mL)	Patient Type	Outcome
de Boer RA et al. ³⁵ (COACH Study)	592	Inpatient	<i>Galectin-3 Assay™</i> , BG Medicine Inc, Waltham, MA. Quartile 1 (5-15.2), quartile 2 (15.2-20.0), quartile 3 (20.0-25.9), quartile 4 (25.9-66.6)	HF	Doubling of galectin-3 level was associated with death or HF admission (HR 1.97, 95% CI, 1.62-2.42)
Lok DJ et al. ³³ (DEAL-HF Study)	232	Inpatient	<i>Galectin-3 Assay™</i> , BG Medicine Inc. Quartile 1 (< 13.63), mean 11.3; quartile 2 (13.63-17.63), mean 15.5; quartile 3 (17.64-21.62), mean 19.5; quartile 4 (> 21.62), mean 28.2	Chronic HF	Galectin-3 level was associated with increased HR for mortality (HR 1.24, 95% CI, 1.03-1.50; $P = .026$)
van Kimmenade RR et al. ³¹ (PRIDE Study)	599	Emergency department	<i>BMS279/2</i> , Bender MedSystems, Vienna, Austria. Galectin-3 median and interquartile range in HF patients = 9.2 (7.4-12.1); in non-HF patients = 6.9 (5.2-8.7)	Acute HF	Elevated galectin-3 level was best independent predictor of 60-day mortality (OR 10.3; $P < .01$) and 60-day death/recurrent HF (OR 14.3; $P < .001$)
Shah RV et al. ⁴⁴	115	Emergency department	<i>Galectin-3 Assay™</i> , BG Medicine Inc. Galectin-3 median and IQR in acute decompensated HF = 15.0 (11.1-19.7); galectin-3 median in patients without acute decompensated HF = 11.0 (9.1-14.4)	Acute dyspnea	Dyspneic patients with HF and galectin-3 levels > median value had a 63% mortality; patients with < median value had a 37% mortality ($P = .003$)
Lok DJ et al. ³³ (DEAL-HF Study)	182	Inpatient	<i>Galectin-3 Assay™</i> , BG Medicine Inc. Quartile 1 (< 13.63), mean 11.3; quartile 2 (13.63-17.63), mean 15.5; quartile 3 (17.64-21.62), mean 19.5; quartile 4 (> 21.62), mean 28.2	Chronic HF	Galectin-3 level was positively correlated to a change in LVEDD ($r = 0.20$; $P = .006$)
Sharma UC et al. ²⁹	22	Inpatient	N/A	Cardiac biopsy of aortic stenosis patients undergoing aortic valve replacement	Higher myocardial galectin-3 mRNA expression on hypertrophied hearts with impaired EF compared with compensated forms of hypertrophy (7.08 ± 1.17 vs 4.60 ± 0.51 ; $P < .05$)
Grandin E et al. ⁴⁶	100	Inpatient	<i>Galectin-3 Assay™</i> , BG Medicine Inc. HF patients had galectin-3 level median and IQR (16.7, 14.0-20.6) vs (14.6, 12.0-17.6)	ACS	Galectin-3 was associated with risk of HF after ACS (OR = 1.4, 95% CI, 1.1-1.9; $P = .02$)
Lin YH et al. ³⁴	106	Outpatient	<i>BMS279/2</i> , Bender MedSystems. Galectin-3 level median and IQR = 9.7 and 7.5-12.6, respectively	Chronic HF	Log galectin-3 was significantly correlated with log PIIINP ($P = .006$), log TIMP-1 ($P = .025$), log MMP-2 ($P = .016$), and functional class ($P = .034$)

(Continued)

Table 1
Summary of Clinical Studies Measuring Galectin-3 in Heart Failure (*continued*)

Study	Sample Size	Study Setting	Galectin-3 Level (ng/mL)	Patient Type	Outcome
Tang WH et al. ⁴⁷	178	Inpatient and outpatient	<i>BMS279/2, Bender MedSystems.</i> CHF cohort galectin-3 mean and median = 14.8 ± 4.0 and 13.9 (IQR 12.1-16.9); advanced decompensated HF cohort mean and median = 14.7 ± 4.0 and 14.7 (IQR 12.1-17.0)	Chronic HF and advanced decompensated HF	Higher galectin-3 was associated with poor renal function (eGFR, $r = -0.24$; $P = .007$; cystatin C, $r = 0.38$; $P < .0001$) and predicted all-cause mortality (HR 1.86, 95% CI, 1.36-2.54; $P < .001$)
Ueland T et al. ⁴⁸	168	Outpatient	<i>Galectin-3 Assay™, BG Medicine Inc.</i> Galectin-3 level was dichotomized at median ≤ 15.3 and ≥ 15.3	Chronic HF	Galectin-3 level was associated with increased unadjusted HR for mortality (HR 1.41, 95% CI, 1.00-1.99; $P = .49$)
Smith A et al. ⁴⁹	2252	Laboratory sample analysis	<i>Galectin-3 Assay™, BG Medicine Inc.</i> AMR was up to 96.6 ng/mL; LoD = 1.13 ng/mL and LoQ = 1.32 ng/mL	Serum and EDTA samples from normal subjects and HF patients	There was < 0.5% crossreactivity toward other isoforms (galectin 1, 2, 4, 7, 8, 9, and 12) and collagen (I and III); the galectin-3 assay can be used to measure the galectin-3 levels in both serum and EDTA plasma serum and EDTA plasma samples
Muntendam P et al. ⁵⁰	1092	Laboratory sample analysis	<i>Galectin-3 Assay™, BG Medicine Inc.</i> Galectin-3 mean value = 12.4 ng/mL, SD = 4.4 ng/mL; median = 12.0 ng/mL; central 95% reference interval, 3.8-21.0 ng/mL	Healthy volunteers from Biolumi cardiovascular risk study	The central 95% normal reference interval of galectin-3 measured by the galectin-3 assay is 3.8-21.0 ng/mL; galectin-3 was detectable in the plasma of all healthy individuals and exhibited a normal distribution
de Boer RA et al. ³⁰ (PREVEND Study)	7968	Free living	<i>Galectin-3 Assay™, BG Medicine Inc.</i> Total 11.9 (9.0-13.1); 1st quintile 7.7 (7.0-7.26); 2nd quintile 9.4 (9.0-9.8); 3rd quintile 10.9 (10.5-11.3); 4th quintile 12.6 (12.2-13.1); 5th quintile 15.6 (14.5-17.7)	General population	There were significant, positive associations found for this protein with age, sex, diabetes, hypertension, hypercholesterolemia, BMI, and renal function (all $P < .001$) and smoking ($P = .002$); these associations were somewhat stronger in women than men; the highest quintile of galectin-3 (median 15.6 ng/mL) incurred a 15% 10-year mortality rate compared with a 5% rate for those in the lowest quartile (median 7.7 ng/mL)

ACS, acute coronary syndrome; AMR, analytical measurement range; BMI, body mass index; CHF, congestive heart failure; CI, confidence interval; EDTA, ethylenediaminetetraacetic acid; EF, ejection fraction; eGFR, epidermal growth factor receptor; HF, heart failure; HR, hazard ratio; IQR, interquartile range; LoD, limit of detection; LoQ, limit of quantitation; LVEDD, left ventricular end-diastolic diameter; MMP, matrix metalloproteinase; mRNA, messenger RNA; OR, odds ratio; PLINIP, amino-terminal propeptide of type III procollagen; TIMP-1, tissue inhibitor of metalloproteinase-1.

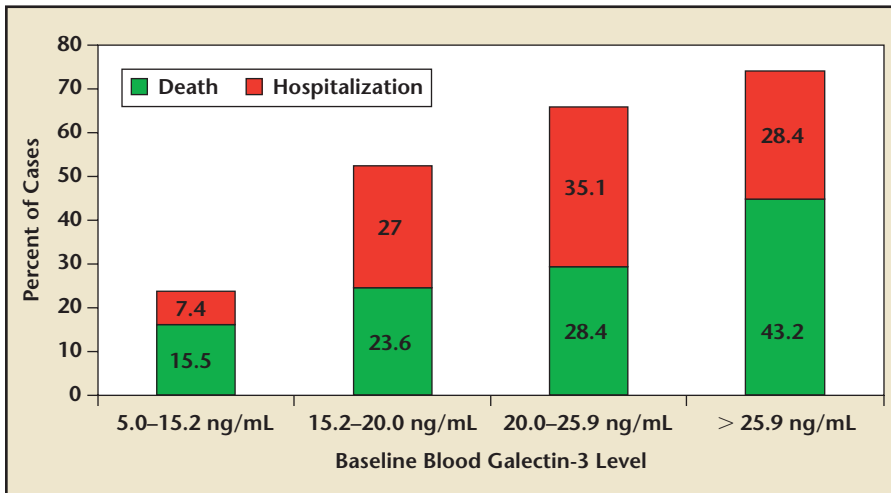


Figure 4. Rates of rehospitalization and death according to baseline galectin-3 levels in the COACH trial. This figure demonstrates the issue of competing mortality (ie, when the galectin-3 level is very high, death is expected before another hospitalization in many cases). COACH, Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure. Reprinted with permission from de Boer et al.³⁵

patients with HF.^{37,38} Natriuretic peptide levels vary widely, but typically project a marked elevation during active decompensation and a reduction with active therapy. It is important to realize that natriuretic peptides, unlike galectin-3, are not pathogenic factors. Cardiac troponin (cTn) assays are useful in HF patients and accumulating data suggest that slight elevations or chronically elevated levels of cTn project a poor outcome.³⁹ cTn T and I are cardiac regulatory proteins that control the calcium-mediated interaction between actin and myosin. Raised cTn levels (with modern high-sensitivity immunoassays) are highly specific for myocyte injury and likely signal current, ongoing myocyte injury and apoptosis in a patient with HF. Like natriuretic peptides, the circulating cTn is not pathogenic and can be viewed as a signal of ongoing damage.

“upstream” signal of the myocardial fibrotic state, ventricular adverse remodeling, and progression of cardiomyopathy. Cardiac fibrosis is an irreversible process; therefore, galectin-3 measurement provides serologic overview of the cumulative fibrotic process in any particular individual. Complementary to the clinical evaluation, BNP, and cTn, galectin-3 levels aid in prognosis, risk stratification, and management. A key difference between other markers is that galectin-3 levels 1) are a direct reflection of galectin-3-mediated cardiac fibrosis, 2) are not acutely changed by HF decompensation, 3) stay elevated once elevated in the majority of cases, 4) indicate the pathologic progression of HF, and 5) are not immediately affected by HF treatment. It has been demonstrated that in those with stable HF, when

6-month hospitalization and death rate (the composite endpoint) is 19.4%.⁴⁰ Conversely, when both measurements are elevated, the 6-month hospitalization and death rate (the composite endpoint) increased to 42.7%. These relationships have been validated by the DEAL-HF study, in which (again) those with both elevated galectin-3 and NT-proBNP had the worst survival compared with those with either marker elevated alone (Figure 5).

The Predictive Role of Galectin-3 in Nonsystolic HF

The predictive power of plasma galectin-3 appears to be predominantly strong in HF patients with nonsystolic HF. Nonsystolic HF (also known as diastolic HF or HF with preserved LV systolic function) is a difficult to characterize entity that causes a high burden of human disease. Nonsystolic HF clearly has a different personality, prognosis, and treatment approach than systolic HF. Currently, nonsystolic HF poses a challenge to diagnose with imaging modalities and the set of associated comorbidities that define these patients (advanced age, lung disease, renal disorders, and/or diabetes).⁴¹ Clearly, a future pathobiologic phenotypic definition of nonsystolic HF is needed to supplement current functional descriptions. It has been shown that angiotensin II directly and via stimulation of aldosterone is a key neurohormone involved in the pathogenesis of cardiac fibrosis and impaired myocardial relaxation.⁴² In one small series, galectin-3 levels were significantly elevated in a cohort of patients with nonsystolic HF compared with control subjects (18 ± 1 ng/mL vs 14 ± 1 ng/mL).⁴³ Thus, if confirmed by future studies, galectin-3, in addition to clinical and echocardiographic findings, may be used to confirm the presence of impaired diastolic function.

Galectin-3 complements other HF biomarkers by providing an “upstream” signal of the myocardial fibrotic state, ventricular adverse remodeling, and progression of cardiomyopathy.

Galectin-3 complements other HF biomarkers by providing an

galectin-3 (< 17.8 ng/mL) and NT-proBNP (< 848 pg/mL) are low,

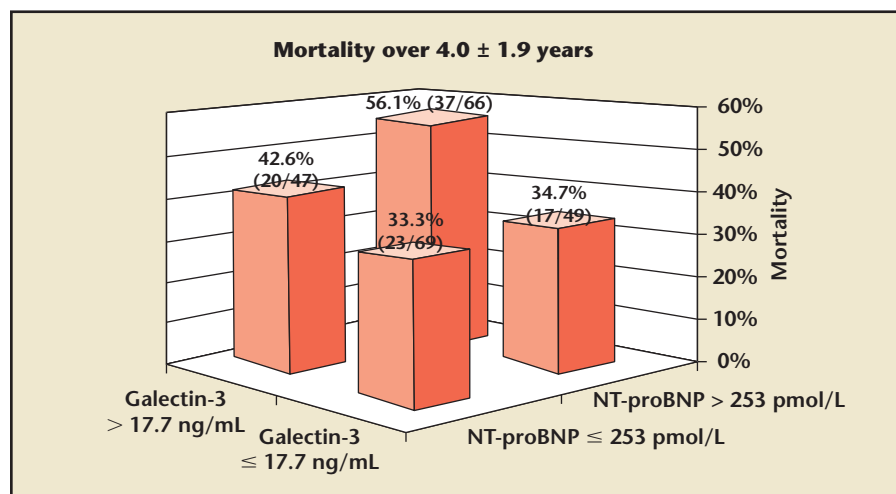


Figure 5. Mortality over a median follow-up of 4 years in patients with class 3 and 4 systolic HF according to baseline galectin-3 and NT-proBNP levels in the DEAL-HF study. DEAL-HF, Deventer-Alkmaar Heart Failure; HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide. Reprinted with permission from Lok et al.³³

Other animal-based and human studies suggest that galectin-3 might provide an early warning marker for individuals who are at risk for the development of nonsystolic HF and may allow early therapeutic intervention. Patients with progressive aortic stenosis and longstanding

hypertension with LVH without overt HF have elevated galectin-3 levels above those of control subjects.⁴³ Similarly, increased expression of galectin-3 is observed in the myocytes of rats with hypertrophied hearts that are sampled by biopsy before the onset of HF.²⁶

The prognostic utility of galectin-3 yields more benefit in patients with nonsystolic HF than those with systolic HF. In 592 hospitalized HF patients from the COACH trial, measurement of galectin-3 levels over an 18-month period provided stronger predictive power for poor outcomes in patients with nonsystolic HF than those with reduced LVEF.³⁵ In a PRIDE substudy, galectin-3 levels exhibited higher degrees of correlation with severity of diastolic dysfunction (higher E/Ea ratio, lower Ea velocity) than any other echocardiographic variable, including LVEF.⁴⁴

Integration of Galectin-3 in HF Management

Data can be integrated from the prospective studies and clinical trials summarized in this article to construct a teachable algorithm incorporating baseline and repeat measurements of galectin-3 in patients with systolic and nonsystolic HF. As depicted in Figure 6, for individuals

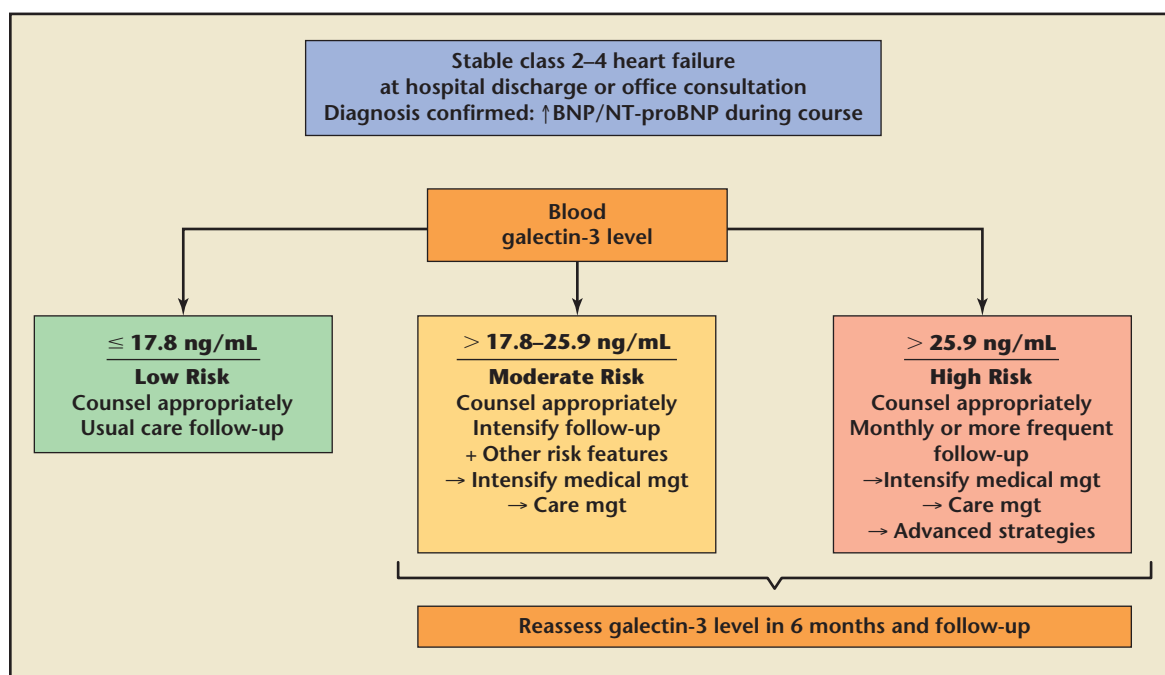


Figure 6. Evidence-based algorithm for the measurement of galectin-3 in patients with HF encountered either in the hospital or office setting. HF, heart failure; Mgt, management; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

who remain in the ≤ 17.8 ng/mL range, continuation of usual care is suggested with periodic outpatient follow-up visits. For those in the 17.9-25.9 ng/mL range, more intensified care management is suggested, given an increased risk of hospitalizations and death with possibly more frequent visits, medication monitoring and adjustment, and added resources considered. Finally, for those with levels > 25.9 ng/mL, there is a very high risk of HF hospitalization and an even greater risk of death. In this group, the most intense resource use could be deployed including HF care managers, home visits, and possibly visiting home physicians. Optimization of medical and device therapy is driven by clinical parameters such as functional class, congestion, edema, LVEF, and QRS duration.⁴⁵ However, those with a galectin-3 level > 25.9 ng/mL face a 28% chance of hospitalization and a 43% risk of death over 18 months; accordingly, they should receive particular attention for optimal care and counseling, in appropriate situations, for end-of-life care.

Conclusions

Galectin-3, a macrophage-derived mediator, induces cardiac fibroblast proliferation, collagen deposition, and ventricular dysfunction. It is the first commercially available blood test measuring a protein that directly participates in the pathogenesis of

HF. Fibrosis is central to both systolic and nonsystolic HF and awareness of galectin-3 levels yields vast potential for management of multiple HF scenarios. HF patients with galectin-3 levels > 25.9 pg/mL or a doubling of galectin-3 from any level face very high rates of hospitalization and death. When the data are considered in aggregate, galectin-3 should be considered as adjunct to the global risk assessment and care management of patients with functional class 2-4 HF. ■

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Main Points

- Galectin-3 is a paracrine and endocrine factor that stimulates macrophages, pericytes, myofibroblasts, and fibroblasts in the heart; it is the first blood test indicating the presence and severity of cardiac fibrosis.
- Galectin-3 is approved as a prognostic aid in the management of patients with heart failure (HF) and is complementary to the clinical evaluation and results of natriuretic peptide testing.
- A galectin-3 level > 25.9 ng/mL identifies an HF patient with over a 70% risk for near-term hospitalization or death.
- Doubling of galectin-3 over the course of 6 months, irrespective of baseline value, identifies a high-risk patient in whom additional care management efforts and advanced therapies could be warranted.

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