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

Conflicts of Interest: None declared.
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Heart Failure Clin 14 (2018) 75–92
http://dx.doi.org/10.1016/j.hfc.2017.08.009

(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

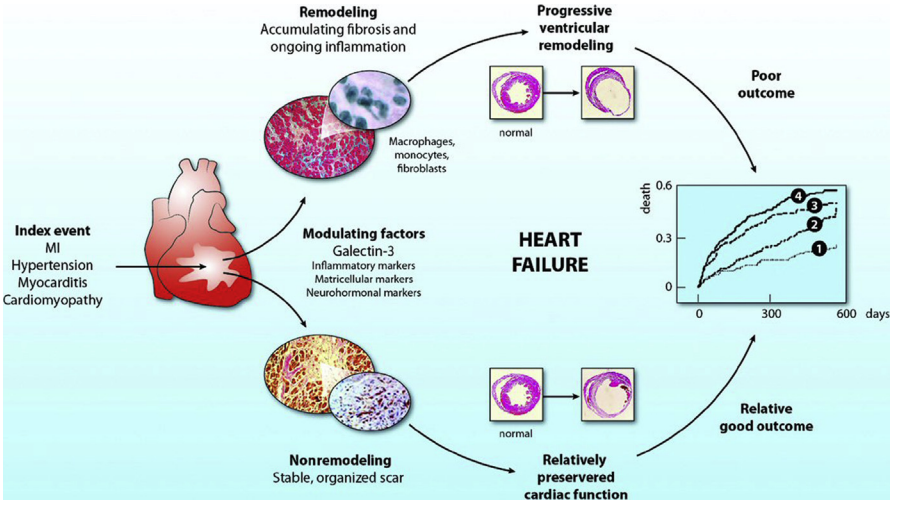

Fig. 1. Mechanism underlying HF. An index event such as a MI, endocarditis, or long-standing hypertension causes stress to the heart. This index event provokes a release of different cytokines that may cause a pathologic remodeling with an upregulation in fibrosis and inflammation; on-going pathologic 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.)