ST2 and galectin-3: ready for prime time?

Wouter C. Meijers, A. Rogier van der Velde, Rudolf A. de Boer

University Medical Center Groningen, University of Groningen, The Netherlands

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Corresponding author:
Rudolf A. de Boer, M.D., PhD, FESC, FHFA
University Medical Center Groningen
University of Groningen
Department of Cardiology
Hanzeplein 1
Groningen, 9713 GZ
The Netherlands
Phone: +31 (0) 50 361 2355
Fax: +31 (0)50 361 5525
E-mail: r.a.de.boer@umcg.nl

ABSTRACT

ST2 and galectin-3 are emerging biomarkers in the field of heart failure and have been extensively studied, and that whether they provide additional prognostic value on top of the clinical models and the gold standard in HF, (NT-pro)BNP. Our aim was to provide a comprehensive review of these emerging HF-related biomarkers in chronic, acute and incident heart failure. Regardless of the type of heart failure, both biomarkers seem to have an additional effect on top of the clinical model including natriuretic peptides. Strategies that combine multiple biomarkers may ultimately prove to be beneficial in the guidance of HF therapy in the future. However, additional prognostic value appears to be limited, and what we need is to prospectively test the consistent observations, which then might lead to the implementation of ST2 and galectin-3 in heart failure algorithms.

1. INTRODUCTION

Heart failure (HF) is a major public health problem and affects more than 25 million patients worldwide. The lifetime risk for development of heart failure (HF) is more than 20% for people at the age of 40 and it is a major cause of morbidity and mortality in the western world (1). Although considerable improvements have been made in HF therapy, 5-year mortality rates remain unacceptably high, exceeding 50% (2). We can expect that, due to an aging population, the prevalence of HF will rise, at an alarming rate (3).

Therefore, better insight in the pathophysiological mechanisms that cause HF is needed. Biomarkers that reflect such mechanisms may assist in risk stratification and may help to create treatment strategies for the individual patient. Biomarkers may aid in the diagnosis of heart failure, or may be used to risk stratify patients, or to guide treatment. As such, numerous biomarkers have entered the heart failure arena. The vast number of biomarker articles has been referred to as a "biomarker tsunami" (4), but most biomarkers are still under investigation as therapeutic consequence and their role in disease management remains unclear at this stage.

The biomarker that is considered the gold standard, and is mentioned as such in HF guidelines, is B-type natriuretic peptide (BNP, or its stable precursor, NT-proBNP); this biomarker has established itself to be useful in diagnosis, prognosis, and disease management (5). In acutely decompensated patients with high volume load, the cardiac wall endures stress resulting in highly elevated BNP levels, which is loading dependent, and therefore will drop after unloading (6). However, BNP has its drawbacks, and is influenced by the "loading status" of the patient during presentation, but also by renal function, and obesity (7-9).

As mentioned by the 2013 American College of Cardiology/American Heart Association guideline for the management of heart failure, both galectin-3 and ST2 are emerging biomarkers that are not only predictive for hospitalization and death in patients with HF, but also add additional prognostic value over natriuretic peptides (10).

## ST2 and galectin-3: basic biology and functions

Suppression of tumorigenicity 2 (ST2), also known as IL1-RL1, is a member of the Toll-like/IL-1 receptor superfamily. As member of this family, ST2 consists of a common intracellular domain, the Toll/Interleukin-1 receptor (TIR). The gene for ST2 is located on chromosome 2q12 and is conserved across species. Four isoforms of ST2 exist namely, sST2, ST2L, ST2V and ST2LV. The soluble (sST2) and the transmembrane (ST2L) are mostly studied in HF research. sST2 lacks the transmembrane and cytoplasmic domains and includes a nine amino-acid C-terminal sequence. ST2 is upregulated by cardiomyocytes and cardiac fibroblasts when mechanical stress is imposed, for instance stretch. The ligand for ST2 is IL-33, another of member of the IL-1 interleukin family. When bound to IL33, ST2L confers an inhibitory effect on the Th2-dependent inflammatory response. Soluble ST2 can bind IL33, and it is hypothesized that sST2 works as a decoy receptor to IL-33 (11) (Figure 1A). Nowadays, it is thought that IL-33 signalling through ST2L provides a cardioprotective phenotype to protect the heart from excess stress, and that sST2 may neutralize this protective effect (12). In this article, we will use ST2 invariably, regardless if we refer to sST2 or ST2L.

Galectin-3 is encoded by a single gene, LGALS3, which is located on chromosome 14. It consists of two domains, namely an atypical N-terminal domain and a C-terminal carbohydrate-recognition domain (CRD). During differentiation of monocytes into macrophages galectin-3 is released and is involved in many processes during the acute inflammatory response such as

Figure 1A,B (Patho) physiological processes of sST2 and galectin-3 in Heart Failure
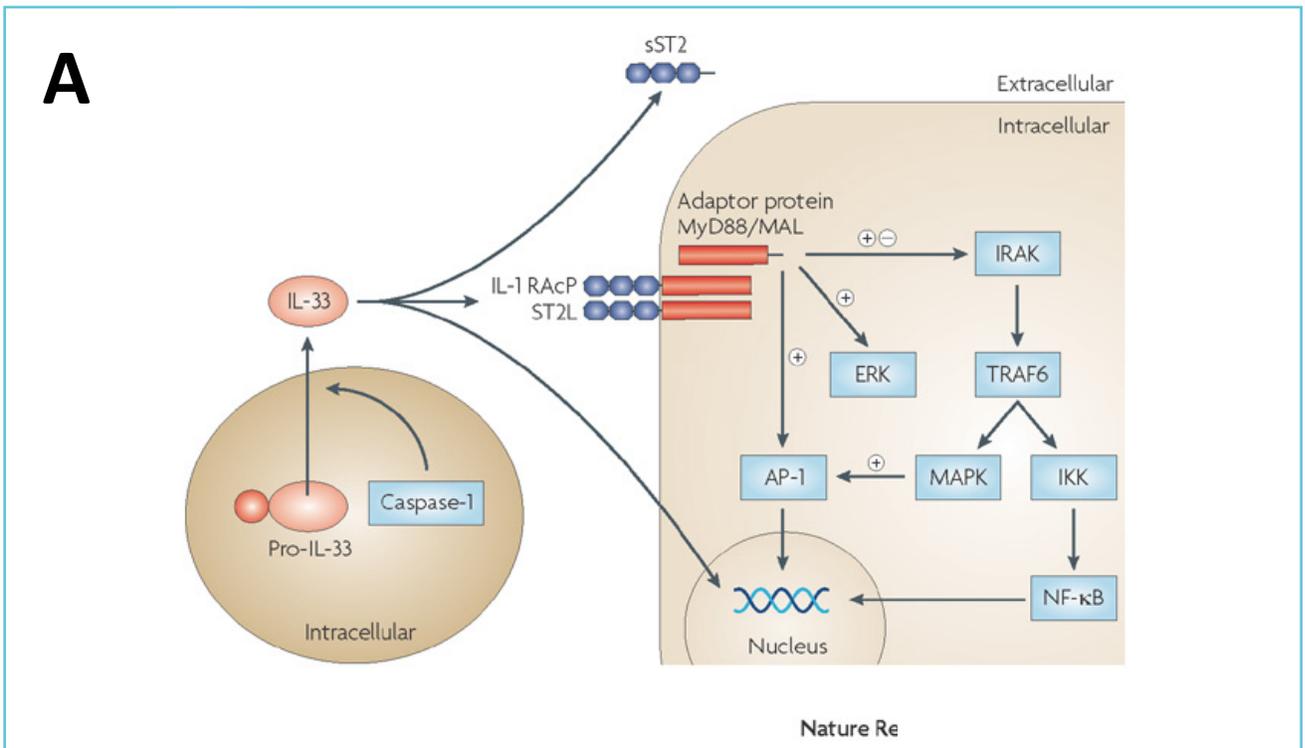
A. sST2 in the extracellular environment might bind free IL-33, thereby effectively decreasing the concentration of IL-33 that is available for ST2L binding and reducing the biological effect of IL-33 (11).
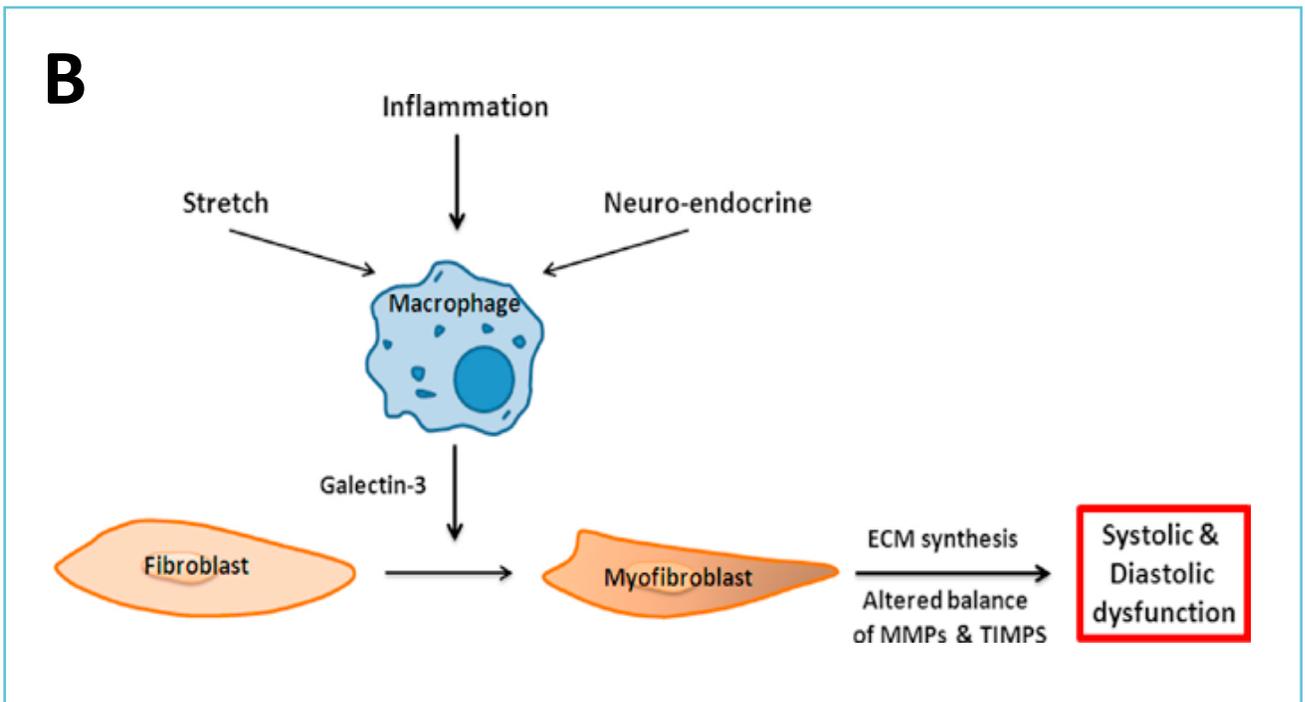
B. The transition of fibroblast to myofibroblast and the involvement of galectin-3 leading to systolic and diastolic dysfunction (35).

neutrophil activation and adhesion, chemoattraction of monocytes, opsonization of apoptotic neutrophils and activation of mast cells. Galectin-3 has been identified as a causal factor in the development of fibrosis of the heart (and other organs). The potential roles of galectin-3 in HF are displayed in Figure 1B (13,14).

Established risk factors, such as New York Heart Association (NYHA) functional class, medication use, routine laboratory values, and left ventricular ejection fraction (LVEF), do not fully explain the mortality risk of patients with chronic HF and do not estimate the prognosis of individuals (15,16). Both ST2 and galectin-3 reflect tissue damage, independent of cardiac loading conditions. As such, they may supplement the currently used biomarkers. We herewith discuss articles describing these emerging HF-related biomarkers in chronic, acute and incident heart failure.

2. CHRONIC HEART FAILURE

2.1. ST2

ST2 can reliably be measured with three different assays. The MBL assay, the R&D assay and the Presage assay. The latter assay is FDA-cleared and CE marked, while the other two methods are research assays. These three methods are not directly comparable and it is important to be informed which method was used when interpreting the results (17). Dieplinger et al. reported that only the Presage ST2 assay meets the needs of quality specification of laboratory medicine (18).

We can only discuss a subset of the published studies, and there are many more. We refer to recent excellent review articles that summarize all the available evidence for ST2 (19-21). Currently, we lack a meta-analysis that would help to compile the aggregate evidence. We discuss a few of the most interesting articles.

One of the first published reports on ST2 and chronic HF was published by Pascual-Figal et al. (22). They demonstrated that ST2 could predict sudden cardiac death in ambulatory patients (N=99) with mild to moderate HF and systolic dysfunction. >70% of sudden cardiac death occurred in patients with both elevated ST2 and NT-proBNP levels compared to 4% when both markers were low (13).

Daniels et al. (23) reported in a larger cohort of HF patients which were referred for echocardiogram (N=588) that heart rate, current diuretic use, estimated creatinine clearance, the presence/absence of right ventricular hypokinesia, and mitral valve E wave velocity were independently associated with ST2 levels. In addition to association analyses, they also observed that multivariate adjusted ST2 levels were significantly predictive for all-cause mortality after one year.

In a much larger study in 2011, Ky et al. (24) reported of 1141 chronic HF patients. The Penn Heart Failure Study (PHFS) investigators concluded that ST2 is strongly associated with HF severity. Patients with elevated levels of circulating ST2 had a markedly increased risk of death or heart transplantation. In the assessment of individual patient risk, ST2 performed equally well compared to the established biomarker NT-proBNP.

The relationship of ST2 and renal function was studied in the Barcelona study (25). This study included 891 patients, and demonstrated that the prognostic value of ST2 was not influenced by renal function. This finding suggests that ST2 may be advocated as a preferable biomarker in patients with renal insufficiency, a co-morbidity that is very common in HF and is among the best predictors of adverse outcomes.

Functional capacity and long-term clinical outcomes in ambulatory patients was studied by Felker et al. (26) in a Controlled Trial Investigating

Outcomes of Exercise Training (HF-ACTION) study. ST2 was measured in a sub-set of 910 patients and was associated with cardiovascular death and HF hospitalization even after comprehensive covariate adjustment. Combining ST2 with NT-proBNP rendered the strongest predictive value (Figure 2A). However, the addition of ST2 to the model did not result in significant reclassification in this study.

Another large trial, the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) study, comprising of 1449 patients, demonstrated the association between ST2 and cause-specific outcomes (27). Next to the primary endpoint (a composite of cardiovascular (CV) death, non-fatal myocardial infarction, and stroke), the authors also studied the association of ST2 with worsening HF. ST2 indeed was associated with the primary endpoint, but was no longer associated after full adjustment including NT-proBNP and CRP, however ST2 remained associated with death due to worsening HF, hospitalization due to worsening HF, and hospitalization due to any CV cause, also after full adjustments. The latter could suggest that the ST2 pathway, in addition to its value in risk stratification of death is also relevant in determining disease progression in HF.

A recent study with a long follow-up of nearly 4 years by Gruson et al. showed in 137 HF patients with reduced LVEF that ST2 predicted long-term CV death, even stronger then NT-proBNP (28).

2.2. Galectin-3

Several commercially available assays can measure galectin-3 plasma or serum levels (29). Manually, galectin-3 can be measured with the BG Medicine assay (30) and the R&D assay (31). But several automated assays are available to measure galectin-3, including the ARCHITECT assay (32), the Vidas assay (33), and an Alere assay. The possibility to measure galectin-3 values on an automated platform allows for a quick, easy and reliable measurement of galectin-3 levels. By far, most published data have been measured with the BGM assay, however the ARCHITECT and VIDAS assays use the same antibodies and are calibrated against the BGM assay, making reported values comparable throughout the literature.

We can only discuss a subset of the published studies, and there are many more. We refer to recent excellent review articles that summarize all the available evidence for galectin-3 (19,34,35). Also, there is a recent meta-analysis that helps to compile the aggregate evidence (36). We discuss a few of the most interesting articles.

Lin et al. observed a correlation of galectin-3 with cardiac extracellular matrix (ECM) turnover markers in 106 CHF patients. These correlations were still abundant after adjusting for age, sex, smoking status and NYHA class (37).

The prognostic importance of galectin-3 was analyzed for the first time in 232 chronic HF patients with systolic dysfunction and severe HF (38). These patients, by Lok et al., were also studied in a follow up study, with 9-years follow-up. After adjustment for several established risk factors, galectin-3 remained an independent prognostic marker for long-term all-cause mortality (Figure 2B) (23,39). Next to this, they observed an independent relationship between galectin-3 and left ventricular remodeling determined by serial echocardiography (24). The latter finding strengthened the hypothesis that galectin-3 is involved in cardiac remodeling. The HF-ACTION investigators did not only measure ST2 as described above, but also measured galectin-3 in a sub-cohort of 895 patients (40). Galectin-3 levels at baseline were related to the primary outcome of the study, all-cause mortality or rehospitalization. Patients with both elevated levels of galectin-3 and NT-proBNP had a two times higher risk for all-cause death or rehospitalization. Galectin-3

Figure 2A,B   sST2 and Galectin-3 combined with NT-proBNP in Chronic Heart Failure
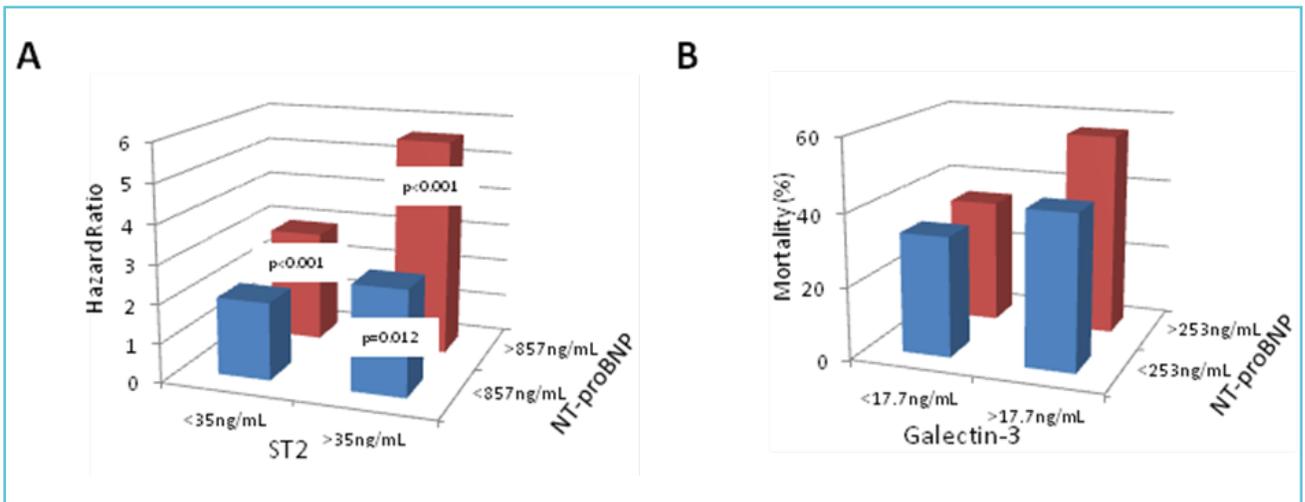
A. Hazard ratio for all-cause mortality based on groups defined by NT-proBNP and ST2, compared with a reference group with low NT-proBNP and low ST2. P values are for change relative to reference group; Figure adapted from Felker et al (26).

B. Mortality rate by galectin-3/NTproBNP subgroups; Figure adapted from Lok et al. (38).

alone lost its predictive value after adjustment for NT-proBNP for the composite endpoint, cardiovascular death or cardiovascular hospitalization. In a more recent analysis of the same study, mortality was divided in death due to heart failure and sudden cardiac death (SCD), and it was shown that galectin-3 had no incremental value on top of clinical factors and NT-proBNP to predict death due to heart failure, while it did add incremental value for the prediction of SCD (41). The low baseline levels of galectin-3 in this cohort could possibly explain this.

In the CORONA trial (42), after a median follow-up of 33 months, galectin-3 univariably predicted the composite endpoint of cardiovascular death, nonfatal myocardial infarction and stroke, but after adjustment for NT-proBNP this was no longer statistically significant. In an additional analysis it was shown that, seemingly paradoxically, patients with low galectin-3 levels may benefit from statin therapy (43). However, in the Val-HeFT trial, originally designed to evaluate the efficacy of valsartan in chronic systolic HF patients, galectin-3 remained significantly associated with mortality and HF

hospitalization, also after addition of both eGFR and NT-proBNP to the model (44). The same results were reported in a smaller trial comprising of 133 CHF patients (45). Galectin-3 seems to be more influenced by kidney function (46,47) than ST2, and it has been shown that elevated galectin-3 levels precede and predict renal insufficiency (48).

In a head-to-head comparison of ST2 and galectin-3 in 876 ambulatory patients, both ST2 and galectin-3 were associated with an increased risk for all-cause mortality but ST2 was only associated with cardiovascular mortality. Galectin-3 did not significantly improve the performance for prediction of mortality when added to a (extensive) base model. The authors discussed that the absence of prognostic value of galectin-3 in this study may be explained by the observation that galectin-3 might confer stronger prognostic information in early disease as compared to progressed disease (49).

Finally, a recent meta-analysis by Chen et al. (36) investigated the relationship between galectin-3 and all-cause mortality in 8,419 participants enrolled in 9 studies, with a follow up

period ranging from 1 to 8.7 years. After correction for well-established risk factors, including in all studies at least age, creatinine (or eGFR) and BNP (or NTproBNP), galectin-3 was shown to have an independent predictive value for mortality in chronic HF.

3. ACUTE HEART FAILURE

Acute HF (AHF) is a main cause of hospitalizations for people over the age of 65 in the western world (50) and a leading cause of mortality. Dyspnea is the most common symptom of AHF patients who are presented at the emergency department (ED) (51). Usually a first assessment of AHF patients occurs at the ED, which commonly consists of clinical parameters that are easy to obtain, such as medical history, use of drugs, signs and symptoms of heart failure, ECG, chest X-ray and laboratory assessment. Currently, biomarker assessment including BNP or NT-proBNP and hs-Troponin is commonly part of this work up. However, despite all these parameters, it has been reported that nearly half of the HF hospitalizations were unnecessary in retrospect (52). This highlights that there is room for improvement. Hospitalization for AHF is a crucial moment in a patients course with the diagnosis, it is estimated that risk for death by 1 year is as high as 30% following discharge, with rehospitalization rates exceeding 50% (53).

3.1. ST2

The first study of ST2 measurement in patients with suspected or proven AHF was in the Pro-BNP Investigation of Dyspnea in the Emergency Department (PRIDE) study (54). In 593 patients admitted to the emergency department with acute dyspnea ST2 was measured. ST2 levels were significantly higher in patients with AHF than patients with non-HF dyspnea and the likelihood for HF diagnosis was greater in patients in the highest deciles of ST2. The sensitivity to

correctly diagnose AHF was significantly better for NT-proBNP than for ST2. ST2 concentrations predicted 1-year mortality in both patients with and without HF, where ST2 showed additive prognostic value on top of NT-proBNP (Figure 3A). In a sub-study of PRIDE in 139 subjects conducted by Shah et al. (55) ST2 concentrations were associated with higher LV end-systolic dimensions and volumes, lower LV ejection fraction, lower right ventricular fractional area change, larger RV systolic pressure and hypokinesia. They also demonstrated that ST2 predicted death at 4 years, independent from other traditional clinical, biochemical and echocardiographic risk markers.

Friões et al. (56) divided AHF patients into HFpEF and HFrEF patients, and reported that NT-proBNP predicted all-cause mortality or readmission at 6 month for both types of patients. Interestingly, ST2 was reported to be a significant marker for prognosis in HFrEF patients, but not so in HFpEF patients. However, in a pooled analysis of three cohorts from Boston, Massachusetts, Linz, Austria and Murcia, Spain, data were available for 447 patients with AHF. They found equally strong prognostic value of ST2 irrespective of LVEF (57). The data suggest that different pathways for the establishment and progression of HF are present, and biomarkers might help to characterize between these phenotypes.

3.2. Galectin-3

As for ST2, galectin-3 was initially evaluated in the PRIDE study published by van Kimmenade et al. (58). They demonstrated that galectin-3 was a better prognostic predictor for 60-day mortality compared to NT-proBNP and that the combination of both predicted mortality even better (Figure 3B). This finding was strengthened by the comparable observations in the Coordinating study evaluating Outcomes of Advising and Counseling in Heart Failure

Figure 3A,B sST2 and Galectin-3 combined with NT-proBNP in Acute Heart Failure
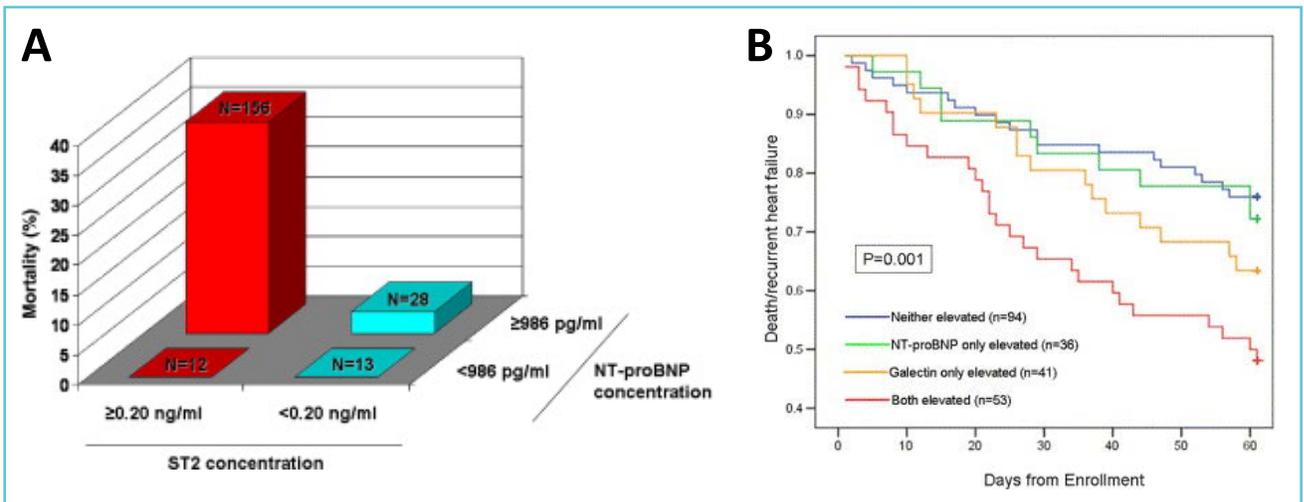
A. Mortality rates at 1 year as a function of ST2 and NT-proBNP concentrations among patients with acute HF (n = 208) (54).

B. Elevated galectin-3 and NT-proBNP levels were in acute heart failure associated with higher rates of mortality/recurrent heart failure (60).

(COACH) study that enrolled 592 AHF patients at discharge (59). In the COACH study galectin-3 seemed to have particularly strong predictive value in patients with HFpEF, compared to patients with HFrEF (59). This finding was validated in a PRIDE sub-study which included echocardiographic data showing significant relations between galectin-3 and diastolic echo parameters. Galectin-3 was significantly correlated with parameters of diastolic function such as E/E' (60). Another large HFpEF cohort comprising 419 patients admitted with AHF, demonstrated the same predictive value of galectin-3 in patients with HFpEF. Galectin-3 emerged as an independent predictor of unfavorable outcome (mortality and HF hospitalizations), and addition of galectin-3 to base models increased c-statistics and yielded significant reclassification indices. The particularly strong value in HFpEF is promising, as currently, the diagnosis and therapy of HFpEF are difficult and further insight in possible mechanism are needed (59).

Further, Meijers et al. showed that the predictive value of galectin-3 is particularly useful for short-term outcomes. Elevated galectin-3 was strongly associated with near-term rehospitalization at 30, 60, 90 and 120 days in a pooled analysis comprising three AHF studies (PRIDE, COACH and the Maryland-study (UMD-H23258), totaling 902 AHF patients (61). In this study, galectin-3 showed numerically very high and statistically very strong reclassification indices.

Another large study focusing on short-term outcome of 603 patients presenting with acute dyspnea in the emergency department showed that galectin-3 was a strong predictor of 90-day outcome. However, in a multivariable model it lost its predictive value (62).

Finally, while most studies report on identification of high-risk patients, Meijers et al. recently assessed whether biomarkers could be used for low-risk prediction in AHF patients. Out of a large panel of biomarkers galectin-3 was the only biomarker able to predict low-risk for all cause mortality and/or HF rehospitalization adjusted for multiple variables including NT-proBNP (63).

4. INCIDENT HEART FAILURE

Despite significant progress in the treatment of heart failure (HF), the incidence and prevalence of this diagnosis are rising. This trend is expected to continue and is attributed primarily to the increasing proportion of elderly in the population, improved care of acute heart diseases resulting in improved patient survival, and increasing prevalence of cardiovascular risk factors such as obesity and diabetes. Biomarkers might identify subjects at risk for incident HF.

4.1. ST2

Four community-based cohorts have examined ST2 concentrations at baseline namely the FINRISK97 population cohort (64), Framingham Heart Study (65), the Dallas Heart Study (66), and the Cardiovascular Health Study (67).

Hughes et al. investigated the predictive value of ST2 in a large Finnish general population study (N=8444). In this cohort of healthy individuals, ST2 adds little predictive information beyond standard risk markers for cardiovascular endpoints, such as MACE, CVD and stroke, and is of marginal benefit to all-cause mortality prediction in a general population of healthy participants. ST2 also failed to improve prediction for heart failure either as an individual marker following adjustment for Framingham risk factors or in addition to the established cardiac marker NT-proBNP and/or eGFR.

In contrast, in 3,428 Framingham participants followed for approximately 11 years, sST2 was associated with both incident heart failure and all-cause mortality. Subjects in the highest quartile of sST2 had a 2.5-fold increased risk of incident heart failure compared with those in the lowest quartile.

ST2 was also measured (using a less sensitive research-use-only method) in 3,294 participants of the Dallas Heart Study, who were followed for a median of 8 years. In this analysis, most subjects did not have measurable sST2. In contrast to data from other cohorts, ST2 concentrations were not associated with most traditional cardiovascular risk factors. Since the assay used in the Dallas Heart Study differs so strongly from the ones used in other studies, it is difficult to compare the studies.

Most recently, ST2 concentrations were measured in 3,915 participants of the Cardiovascular Health Study free of heart failure. During a median follow-up of 15 years, ST2 concentrations at baseline predicted incident cardiovascular events in multivariable-adjusted analyses. Specifically, participants in the upper quintile of sST2 had a greater risk of heart failure and cardiovascular death compared with participants in the lowest quintile.

4.2. Galectin-3

Six community-based cohorts have examined galectin-3 concentrations at baseline, namely the Framingham Heart Study (68), the Physician Health study (case control) (69), the PREVEND study (70), FINRISK97 population cohort (71), the Rancho Bernado study (72), and the Cardiovascular Health Study (67).

In the Framingham (offspring) study, galectin-3 levels were available in 3,353 participants, who were observed during a mean follow-up of 11 years. Galectin-3 was a significant predictor of HF risk, also after multivariable adjustment. This observation was validated in the Physicians' Health Study, which used a case-control design, describing 462 cases and 462 controls. After adjusting for clinical variables there was a significant relation between galectin-3 and new onset HF.

The Physicians' Health Study validated the Framingham findings in a nested case control design, including approximately 900 subjects. After adjusting for BMI, diabetes, AF, hypertension, CRP, alcohol and smoking there was a significant

relation between galectin-3 and new onset HF, with or and without prior CHD.

In the PREVEND (PREvention of Vascular and End stage ReNal Disease) study, a total of 8,569 subjects were followed during a median follow-up of 13 years. Galectin-3 emerged as a predictor of new onset HF in subjects with high CV risk compared to subjects with low CV risk.

The same cohort as described earlier, the general population-based FINRISK 1997 cohort evaluated the usefulness of galectin-3. They observed that galectin-3 levels were predictive for future cardiovascular events, also after adjustment for gender. However, the reclassification indices were modestly improved.

In an elderly cohort (mean age 70 years), the Rancho Bernardo Study, baseline galectin-3 levels were independently associated with all-cause and CVD mortality. These elderly subjects had no known CVD prior to the study participation. Addition of galectin-3 to the model resulted in significant reclassification indices.

Both ST2 and galectin-3 was measured in the Cardiovascular Health Study. Comparable results for both biomarkers were observed and subjects in the upper quintile of galectin-3 level had a greater risk of heart failure and cardiovascular death compared to participants in the lowest quintile.

5. THERAPEUTIC GUIDANCE

Serial ST2 sampling over time during aggressive HF therapy seems to be a strong prognostic indicator for future outcomes (73). Especially adjustment of β-blocker dose might be associated with changes in ST2 levels (74). In a post hoc analysis from the PROTECT trial (75), it was observed that β-blocker therapy exerted beneficial effects across the complete study population. Patients with high ST2 levels and a low dose of β-blocker were at the highest risk for cardiovascular events. However, up-titration of beta-blocker therapy nowadays is part of the standard clinical care so it is questionable if we would need a biomarker-guided treatment.

Next to an association with β-blockers an association for both biomarkers with mineralocorticoid receptor antagonists (MRAs) is present. Recent experimental data showed that MRA treatment after MI strongly reduced both galectin-3 and ST2 expression in the myocardium and improved LVEF (76). Aldosterone might play a role as mediator of the pro-fibrotic effects of galectin-3. However in clinical studies (77,78) no evidence of the interaction between galectin-3 and MRA treatment were observed. Therefore, it remains unclear whether we should use biomarker-guided therapy in the future.

6. TARGETED THERAPY

Unraveling the pathophysiological mechanism of both biomarkers could be of significant importance. As already described and proven in experimental studies, galectin-3 inhibitors, such as complex carbohydrates, attenuate the cardiac remodeling processes and reduce fibrosis formation after different cardiac stressors (79,80). These inhibitors also resulted in improved function parameters as fractional shortening. Galectin-3 has the potential as a new modifiable risk factor in HF patients and it would be very interesting to monitor galectin-3 levels pre and post anti-galectin-3 treatment (81). No such data exist for ST2.

7. CONCLUSION – READY FOR PRIME TIME?

We have provided an overview of the potential value of ST2 and galectin-3 in chronic heart failure, acute heart failure and incident heart failure. Both ST2 and galectin-3 show prognostic value in mostly all patients with chronic and acute HF, on top of natriuretic peptides.

As clearly shown in all figures, both sST2 and galectin-3 predict outcome more accurately when combined with NT-proBNP. These consistent findings may pave the road for the implementation of sST2 and galectin-3 in chronic heart failure algorithms. Strategies that combine multiple biomarkers may ultimately prove beneficial in guiding HF therapy in the future.

This is also true for AHF patients, but in this setting even serial measurements of both galectin-3 and sST2 would provide further insights in patient management strategies, for example at discharge and 3-6 months later during the "chronic" state of the disease.

When considering risk assessment, there is no urgent need for additional prognostic tests. Current models already very accurately predict prognosis in our HF patients, and addition of more factors show modest improvement of the models. We do not need biomarkers to tell us to take medication that is part of evidence-based therapy, which we should start and up titrate in all HF patients.

So, the most challenging task will be to design, fund and launch prospective studies that incorporate biomarker based treatment algorithms. Such studies will provide definite data as to whether it is useful and economical to order (expensive) biomarker tests on the long run. Such studies should test biomarker specific or targeted therapies, not the state of the art medication that is part of daily care. Only in this manner, HF management will move forward towards more personalized approaches, which might lead to the use of multiple biomarkers. Learning the most efficient ways to exploit them to assess and risk stratify patients should be the goal of the upcoming years. Testing algorithms including ST2 and or galectin-3 could be a first step towards more personalized medicine.

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