

## Review Article

# A biomarker guided approach in heart failure

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**Abstract**

Heart failure is one of the commonest diagnoses presenting to physicians in the community or hospital care. Symptoms are often subjective, with clinicians having to rely on clinical assessment and radiological imaging to manage these patients. Treatment is often symptomatic with no clear therapeutic goals as yet identified. To date, there are no objective measures to diagnose, predict, prognosticate or guide therapy in compensated and decompensated heart failure, which is why a novel biomarker guided management approach is gaining so much momentum in the clinical community. This review encompasses recent data on this new approach and details on the potential clinical benefits of the most widely studied cardiac biomarkers currently available.

**Key Words**

Acute Decompensated Heart Failure, Biomarker, Remodelling, Prediction, Prognosis, Risk Stratification

**What is a biomarker?**

The term biomarker was first introduced in 1989 and was defined as a ‘*measurable and quantifiable biological parameter which is used to assess health and physiology in a patient in terms of disease risk and diagnosis*’’. This definition was later amended in 2001 by a National Institute of Health (NIH) working group as an ‘*objectively measured parameter that is an indicator of normal biological processes, pathogenic processes or as a response to pharmacological therapy*’’.<sup>1</sup> Ever since the concept’s birth, its potential prospects are slowly gaining momentum in the medical community.

**Biomarkers: The new paradigm in heart failure**

Heart failure (HF) symptoms are often very misleading and subjective, particularly if not associated with signs of fluid overload. In spite of better resources, there are limited tools at the physician’s disposal to objectively diagnose and follow up this ever growing pathological entity. The genomic changes associated with the physiological factors involved, contribute to multiple molecular, cellular and interstitial changes. These changes occur as a result of chronically activated response systems. Signs of cardiac de-compensation happen when remodelling is excessive.

HF is a complex multi-system disorder (Figure 1) characterised by abnormalities in cardiac myocytes, altered renal function and neurohormonal changes. All these act as compensatory mechanisms to maintain adequate cardiac output in the presence of cardiac insults. Neurohormonal systems (renin-angiotensin (RAS), sympathetic (SNS) and arginine-vasopressin (AVS) systems) are activated to increase myocardial contractility, heart rate, peripheral vasoconstriction and promote salt and water retention. When these systems fail to compensate, various structural changes take place in the myocardium. Fluid overload because of worsening cardiac output results in myocardial stretch and release of natriuretic peptides (NPs). Oxidative stress and myocardial injury take place when vascular supply is disproportionately low compared to demand. Recurrent cell damage up-regulates certain inflammatory and remodelling mediators at the point of decompensation. Modelling mediators like galectin-3, soluble ST2 (sST2), matrix metalloproteinases (MMP), tumour necrosis factor alpha (TNF- $\alpha$ ) and endothelin stimulate a number of signal transduction cascades. The consequent myocyte hypertrophy, fibroblastic activity and apoptosis,

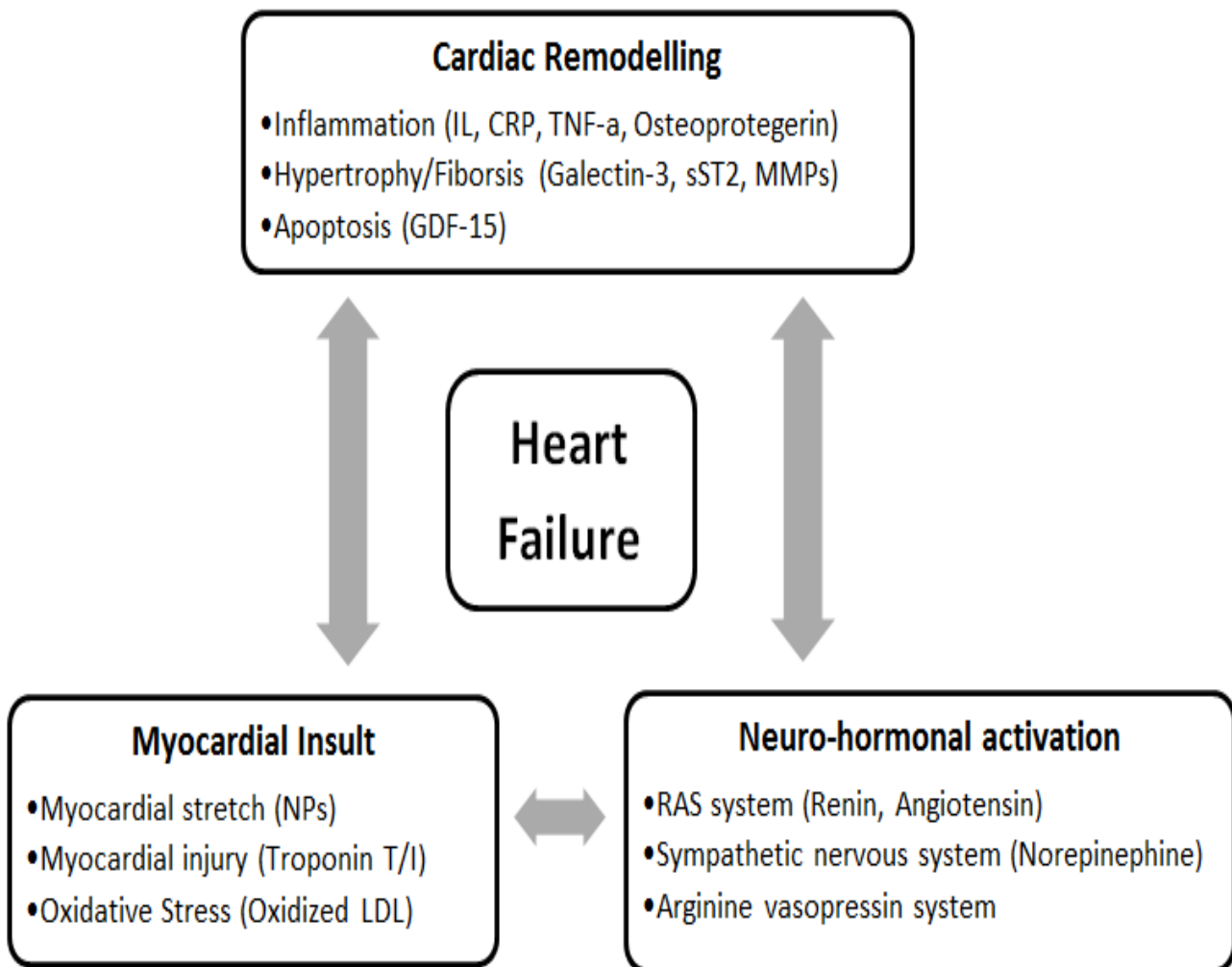
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give rise to a vicious cycle of cardiac structural remodelling. The capillary versus myocyte mismatch in response to these structural changes worsens myocardial dysfunction, decreasing cardiac chamber compliance and diastolic dysfunction.

Such insights into the pathophysiology of HF have brought about promising advances in the discovery and clinical utility of specific cardiac biomarkers. If used wisely, cardiac biomarkers can be used as i) prognostic predictors (predict onset or worsening of HF), ii) objectively diagnose compensated or decompensated HF, iii) risk stratify patients, iv) develop new specific target therapy (at the biochemical level) or v) as a biological tool to guide therapy.<sup>2</sup>

Understanding the physiological pathways and functions of biomarkers (Figure 1) will help clinicians better understand the potential of these biomarkers in the clinical field. Whilst most of the available biomarkers are still in their infancy in terms of their roles and clinical utility in heart failure, NPs, galectin-3, sST2, growth differentiation factor-15 (GDF-15) and troponin T are showing potential in this field. NPs definitely stand out, with the markers most studied and utilised in biomarker guided HF management. In the following sections, a closer look is taken in the various biomarkers available, all of which will be discussed separately in the next sections.

**Figure 1:** Pathophysiological pathways of cardiac biomarkers in Heart Failure



\*Abbreviations: IL (Interleukins), CRP (C-reactive peptide), TNF-a (Tumour Necrosis Factor alpha), MMPs (Matrix Metallo-proteinases), GDF-15 (Growth Differentiation Factor), NPs (Natriuretic Peptides), LDL (Low density lipoprotein), RAS (Renin-Angiotensin System)

### Natriuretic Peptides (NPs)

NPs including brain natriuretic peptide (BNP), N-terminal pro-Brain Natriuretic Peptide (NT-proBNP) and adrenomedullin (ADM) are peptides released in response to myocardial strain (particularly atrial stretch) during fluid overload. This is the case in acute decompensated HF (ADHF). These peptides work by promoting vasodilation, natriuresis and diuresis. Both BNP and NT-proBNP are released in their precursor form.<sup>3</sup> The short half-life and disease dependent fluctuant levels make NPs very useful in the management of dyspnoeic patients. ADM on the other hand, has a very short half-life hence making it a poor predictive biomarker. Its precursor MR-proADM has a longer half-life, overcoming ADM's problem in this regard. According to the multicentre BACH trial,<sup>4</sup> MR-proADM was deemed non-inferior to BNP.

NPs have been extensively studied as objective diagnostic markers of HF. A high value in an acutely dyspnoeic patient can be used to quantify acute decompensated heart failure (ADHF) severity whilst a low value (<100pg/mL of BNP) effectively excludes ADHF as a differential for acute dyspnoea due to its excellent sensitivity (96.98% as per *BACH* Trial).<sup>4</sup> Whilst high values might possibly reflect ADHF, one should adjust levels for renal dysfunction (higher baseline) and obesity (lower baseline). Of note, natriuretic peptide levels may be relatively low in patients presenting with flash pulmonary oedema, often because a short time interval precedes the up-regulated de-novo peptide synthesis after natriuretic peptide stores are acutely depleted.<sup>5</sup>

All the NPs are independent predictors of future cardiac events and hospitalisations as stated in the *Val-HeFT* trial.<sup>3</sup> Such markers can be used to help identify those at risk patients who would benefit from an earlier follow up and tighter risk factor control.

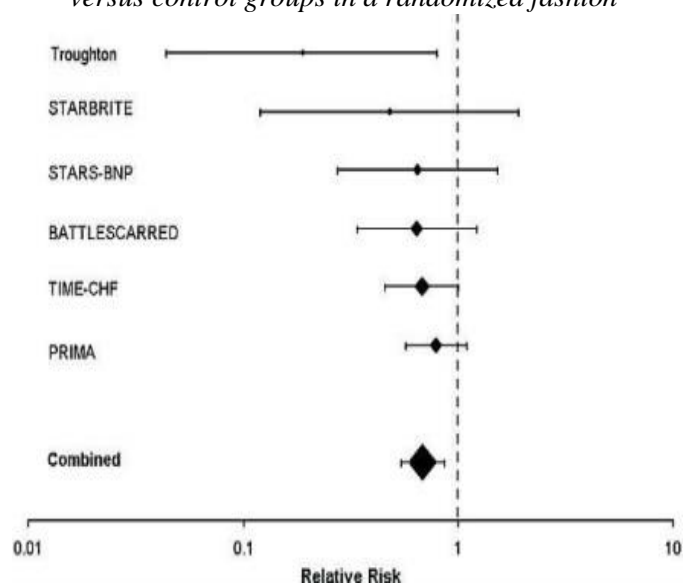
There is significant potential with the use of natriuretic peptides as prognostic markers. The *IMPROVE-CHF* study confirmed the usefulness of these peptides (NT-proBNP in particular) in the management of the acutely dyspnoeic patient.<sup>6</sup> Other studies have particularly shown their usefulness as mortality predictors with a high BNP associated with a 3-4 fold mortality in the *ADHERE* trial results. This benefit is best seen with NT-proBNP, regarded as the best predictor out of all the natriuretic peptides, itself improving the prognostic value of MR-proANP when used in combination).<sup>3</sup> Besides reducing in-patient mortality with relative falls in natriuretic peptide levels, the clinical usefulness of these proteins extends to outpatient mortality. The absolute NP level at discharge seems to have an excellent evaluation of ventricular function. A high level of natriuretic peptide indicates the absence of a complete optivolaemic status and is

associated with a higher risk of hospitalisation after ADHF, particularly in the region of 600-700-pg/ml for BNP and >7000 pg/ml for NT-proBNP.<sup>7</sup>

These markers are said to be the pioneers in a biomarker guided therapeutic approach, widely used to assess fluid overload in HF patients. Studies show that angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), diuretics, spironolactone and perhaps long term beta-blockers (levels increase with short term beta-blockade) actually decrease natriuretic peptide levels. Several small studies and a recent meta-analysis (Figure 2) including the *Troughton*, *STARBRITE*, *STARS-BNP*, *BATTLESCARRED*, *TIME-CHF* and *PRIMA* Trials by Felker et al in 2009 suggest overall improved clinical outcomes with a biomarker guided approach using NPs. That said, one should interpret results with caution as some of these trials had wide confidence intervals for the hazard ratios, most crossing the line of no effect.<sup>8</sup> The on-going *GUIDE-IT* randomised control trial might yet reveal the usefulness of such an approach though at this point, actual data on the benefit is still lacking.<sup>9</sup>

Knowledge of a patient's baseline peptide levels may further improve diagnostic accuracy, reason being that high levels may actually be the patient's optivolaemic (dry) level due to persistent myocardial strain, even after resolution of the acute exacerbation. In any case, serial levels can be very useful in both in-patient and out-patient settings. To gain full advantage of their clinical applicability, the caring physician should aim at decreasing NP levels present during the acute volume overload (wet) phase down to optivolaemic (dry) levels.<sup>5</sup>

**Figure 2:** Forest plot of all-cause mortality among patients with heart failure in biomarker guided therapy versus control groups in a randomized fashion<sup>8</sup>



**Soluble ST2 (sST2)**

ST2 is part of the Interleukin-1 (IL-1) receptor family, the gene coding for a trans-membrane receptor (ST2L) and soluble form (sST2). The ligand of ST2 (IL-33) is involved in reducing fibrosis and hypertrophy in mechanical strain. Studies have shown that excess sST2 is involved in cardiac hypertrophy, fibrosis, ventricular dilatation and reduced ventricular contractility. Iatrogenic sST2 administration blocks the anti-hypertrophic influences of IL-33 in a dose dependent fashion, highlighting its possible involvement in the pathogenesis of HF.<sup>10</sup>

sST2 levels are higher in ADHF when compared to control, increasing with worsening severity and reduced left ventricular ejection fraction (LVEF), making it a useful diagnostic tool.<sup>3</sup> Besides being associated with decompensation, high levels in a healthy asymptomatic population are also able to predict a worse cardiovascular morbidity. Correlation analysis in the Framingham heart study showed that age, sex, diabetes and hypertension were highly correlated with sST2 meaning that baseline levels should be interpreted accordingly.<sup>10</sup> The potential of sST2 as a predictor biomarker is quite significant and was found to be non-inferior to NT-proBNP in mortality prediction. The majority of cardiovascular events occur when both biomarkers are elevated, meaning that a combination of ST2 and NT-proBNP might synergistically increase their prediction abilities.

The potential for sST2 as a prognostic biomarker has been suggested after the results of the *PROTECT* study. Higher baseline sST2 values during ADHF and chronic HF were associated with future cardiovascular events (HF hospitalisation and cardiovascular death).<sup>10-11</sup> The *PREDICT* Trial also showed that sST2 is the strongest predictor of death at four years in patients with acute dyspnoea, bypassing even the NPs. High baseline levels of sST2 were also associated with death or new congestive HF in acute myocardial infarction patients in the *TIMI-14* and *ENTIRE-TIMI-23* trials, meaning that sST2 may one day also be used to predict heart failure after myocardial infarction.<sup>3</sup>

The low intra-individual biological variation of sST2 compared to other cardiac biomarkers offers a significant advantage in its utility for serial testing, as

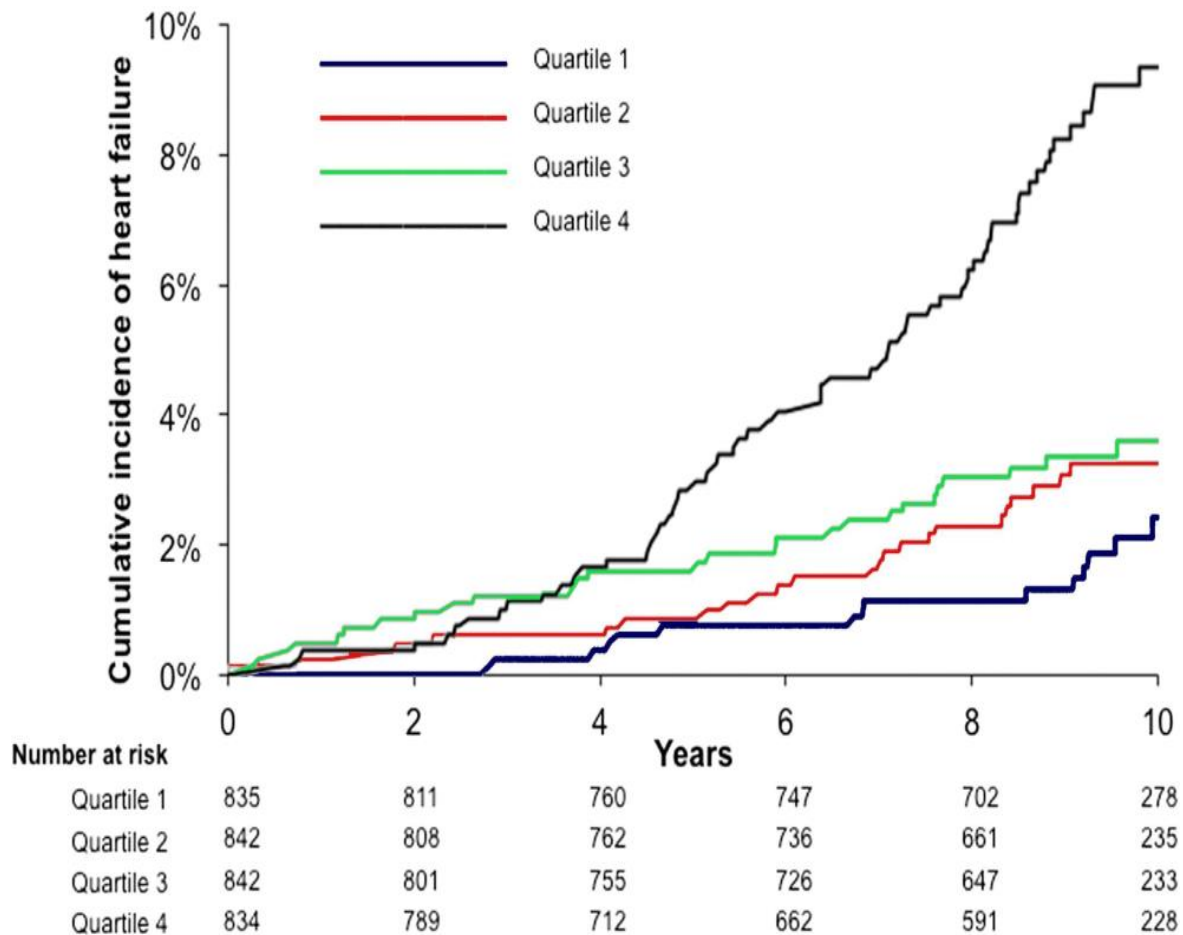
acute changes in blood levels are more diagnostic.<sup>10</sup> In a recently published post hoc analysis of the *PROTECT* study, Januzzi et al hypothesized the potential of sST2 in guiding beta blocker therapy, similar to guiding anti-HF treatment according to NP levels. sST2 decreases when maximizing beta blockade, indicating that the latter in some way interferes with cardiac remodelling by inhibiting sST2, thus improving prognosis. This tends to be most effective in patients with high levels of sST2 at baseline, possibly being of some use in a select cohort of heart failure patients, especially as it mimics decompensated states.<sup>11</sup>

**Galectin-3**

Galectin-3 is another promising biomarker, associated with the cumulative development of fibrosis and apoptosis in cardiac remodelling. Studies in rats have showed that galectin-3 is already high in those with compensated hypertrophy of failure prone hearts. The gene for galectin-3 was the strongest up-regulated gene in ADHF. In this same study, a pericardial infusion of galectin-3 in previously normal rats also induced ADHF, revealing it actually plays a role in the pathophysiology of heart failure, possibly by direct cardio-toxicity or by indirect acute kidney injury.<sup>12-14</sup>

While its expression is maximal at peak fibrosis and virtually absent after recovery,<sup>14</sup> there seems to be no promise as a diagnostic marker of HF, since its expression occurs way before ADHF is clinically evident.<sup>3</sup> Analysis of the Framingham heart study did however provide conclusive evidence that galectin-3 levels in well and asymptomatic patients in the community, accurately predicted an increased risk for future heart failure and mortality (Figure 3). Levels were positively associated with left ventricular mass, with no difference in baseline values present when comparing future ADHF of normal versus reduced LVEF.<sup>15</sup> Results by De Boer et al (2011) who looked at galectin-3 levels in two equal and comparable groups of low or preserved LVEF HF revealed that galectin-3 appeared to be a better prognostic marker in the latter group, with one hypothesizing that it plays a more prominent role in the pathophysiology of preserved LVEF.<sup>16</sup>

Figure 3: The cumulative incidence of heart failure (HF) increasing with higher galectin-3 quartiles<sup>15</sup>



Galectin-3 also has the potential as an important prognostic biomarker during admission with ADHF, predicting death or re-hospitalisation with ADHF after discharge. Plasma levels in patients presenting with acute dyspnoea have a higher 60 day mortality or recurrent admissions with HF, marginally better than NT-proBNP.<sup>17</sup> Both biomarkers complement each other and improve mortality prediction. Higher galectin-3 levels showed a higher four-year mortality rate in patients presenting with ADHF.<sup>14</sup> According to the PROVE-IT-TIMI 22 study, high Galectin-3 levels in patients admitted with acute coronary syndrome predicted the onset heart failure after the index admission.<sup>6</sup> As per the *DEAL-HF* study, its prognostic ability also applies to compensated HF irrespective of New York Heart Association (NYHA) functional class.<sup>18</sup>

Different to other biomarkers, in-vivo studies in animals have shown galectin-3 to be directly involved in the pathophysiology of HF, precipitating ADHF when compensatory measures fail. It is also associated with inflammatory cytokines (CRP), Interleukin-6 (IL-6) and Vascular Endothelial Growth Factor (VEGF) in the overall remodelling pathway, further revealing its role in structural changes in the heart. Treating the cause rather

than the effect of ADHF might someday hold promise in galectin-3 targeted therapies and galectin-3 can someday be used to risk stratifying remodelling (high-risk) versus non-remodelling (low-risk) ADHF. Similarly to the effect of sST2 with beta blockade, future research might develop specific galectin-3 targeted therapies which could hypothetically directly reverse remodelling and treat the cause rather than the effect.<sup>3</sup>

#### Growth Differentiation Factor 15 (GDF-15)

GDF-15 is a member of the transforming growth factor beta (TGF- $\beta$ ) superfamily, expressed in stressful situations including inflammation and remodelling, in an attempt to inhibit myocyte hypertrophy, apoptosis and adverse remodelling [2]. Levels are high in ADHF when compared to a control group, correlated with severity and reduced LVEF, just like sST2. It is particularly diagnostic, as seen in the study by Wang et al also suggesting it can help differentiate reduced from preserved LVEF ADHF.<sup>8</sup> GDF-15 is however non-specific, with high levels also present in severe liver disease, pregnancy and certain cancers.<sup>3</sup>

GDF-15 can be used to help predict mortality and heart failure. Levels also correlate with NT-proBNP in

post-myocardial infarction, possibly implying that it might be useful to risk stratify those patients at risk of adverse cardiac events in the early or late stages after discharge.<sup>19</sup> There are however no studies to date about GDF-15 serial testing and GDF-15 targeted drug therapies.

### Troponin T

Troponin T is a regulatory protein attached to tropomyosin in cardiac myocytes, released in response to myocardial infarction secondary to coronary (atherosclerosis) or non-coronary causes (cytotoxicity, apoptosis and inflammation).<sup>3</sup>

It is a sensitive marker of myocardial injury with levels correlated to the degree of myocardial necrosis, with high sensitivities now available detecting even lower levels. It is however not a specific diagnostic marker for ADHF with high levels also possible in acute kidney injury, sepsis, subarachnoid haemorrhage, amongst others.<sup>3</sup>

Since elevations in Troponin levels are often associated with unclear therapeutic ramifications in the non-acute setting, they are at present not useful for risk stratification or prediction. However, Miller et al demonstrated a higher mortality risk and increased rates of cardiac transplantation in patients with persistently high levels in asymptomatic stable NYHA Class III and IV HF patients.<sup>20</sup>

Troponin T is an independent prognostic predictor of mortality, mimicking NT-proBNP and sST2, with addition of both biomarkers improving prognostic capabilities significantly.<sup>3</sup> There are no studies regarding Troponin T targeted therapies or the management implications of serial testing.

### Conclusion

More studies are needed to fully validate established biomarkers for clinical practice. Better biomarkers are currently needed for diagnosis, screening and monitoring. With the integration of genomic, proteomic, phenotypic and transcriptional profiling, a new era in cardiology of 'personalized medicine' might at some point become a reality.<sup>9</sup>

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