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The usefulness of sST2 and TNF α biomarkers in evaluating the prognosis of patients with heart failure

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Abstract

Background and Aim. Heart failure (HF) remains a major global health burden, marked by high morbidity, mortality, and healthcare costs. While biomarkers such as BNP and NT-proBNP are widely used in diagnosis and management, their limitations have prompted investigation into additional markers. This review focuses on the role of soluble ST2 (sST2) and tumor necrosis factor-alpha (TNF α) in HF, exploring their biological mechanisms, association with inflammation, and potential clinical value.

Methods and Results. A non-systematic literature search was conducted using databases such as PubMed, UpToDate, and ESC resources. Search terms included “heart failure diagnosis,” “biomarkers,” “NT-proBNP,” and “precision medicine.” A total of 48 English and Lithuanian articles published between 2015 and 2025 were reviewed, with emphasis on clinical guidelines and consensus statements from societies such as the ESC and HFSA. NT-proBNP remains the most validated biomarker for HF diagnosis and management. sST2 has demonstrated value in predicting mortality and rehospitalisation, particularly when used with natriuretic peptides. TNF α , though less specific for diagnosis, offers insights into inflammatory activity and HF pathophysiology. Together, these biomarkers support a multi-marker strategy for improved risk stratification.

Conclusion. NT-proBNP remains central to HF diagnosis, while emerging biomarkers like sST2 and TNF α provide complementary prognostic information. Their integration into clinical practice may enhance precision in heart failure care, though further research is needed to confirm their routine use.

Keywords: heart failure (HF), biomarkers, soluble suppressor of tumorigenicity-2 (sST2), tumour necrosis factor-alpha (TNF α), NT-proBNP, natriuretic peptides, cardiovascular disease (CVD), high-sensitivity cardiac troponin (hs-cTn).

1. Introduction

Heart failure could be physiologically simplified and described as the heart's failure to meet the body's demands, resulting in perfusion problems. Heart failure is often a terminal complication of other CVDs that are widely known as the leading cause of morbidity and mortality in many nations worldwide [1]. The evolution of IT and pharmacology has made diagnosing, prognosis and treating HF easier, making it a less fatal condition, thus prolonging average lifespan, growth of comorbidities and risk factors for HF, and more prolonged survival after myocardial infarction [2] Though heart failure is still hard to predict, biomarkers are one of the recently widely-raised and recognised tools that help doctors understand and diagnose it.

In the light of recent studies concerning biomarkers, they are in the current day and age of personalised medicine routinely used by physicians for diagnostics, treatment plans and prognosis [3].

There are already established biomarkers, backed by multiple studies and quality research, that have been passed to be used in HF diagnostics and management. For example, NT-proBNP and hs-cTn have been integrated into the European (European Society of Cardiology, ESC) and American (American Heart Association, AHA) guidelines since 2016. In the ESC guidelines, natriuretic peptides are advocated for their value in the diagnostics of HF, especially in the possibility of excluding HF [4]. However, even if the data and research point to the utility of biomarkers [5], their limitations are usually easily pinpointed. Clinical application of these biomarkers is limited by many factors – including sometimes significant fluctuation at various time points in decision making, whether in the emergency room or the timeframe of inpatient treatment through to discharge [6] or outpatient primary care clinic [7]. Furthermore, other factors have been proven to influence biomarker levels,

including age, sex, individual biological variation, kidney function, etc. [8].

With these limitations in mind, it is no surprise that not many biomarkers have yet made it past the research stage and only a few are regarded as proven and established enough to be used routinely. Given that, this systematic review focuses on two biomarkers that have been very noticeable and have promising viewpoints from several recent studies – sST2 and TNF α .

1.2. Biological Composition

ST2 is a member of the interleukin (IL)-1 receptor family, whose gene is located on human chromosome 2q12. Alternative promoter splicing and 3' processing of the mRNA produce two different forms: a soluble receptor, named sST2, or a transmembrane receptor, named ST2L. ST2 was first described in 1989. The literature mistakenly called ST2 a “suppressor of tumorigenicity 2” when, in fact, the original name it was given was “growth stimulation expressed gene 2”, then renamed “serum stimulation-2”, as it was first discovered to function as a mediator of type 2 inflammatory responses [9]. Its role as a cardiac marker was suggested in 2002 by Weinberg et al., analysing the expression of 7,000 genes in cardiomyocytes undergoing mechanical strain and noting that myocardial transcripts of ST2 increased significantly in response to this stimulus. This is curious and important, as the primary source of sST2 in the circulation in patients with HF does not appear to be the heart. Indeed, it has been shown that type 2 pneumocytes represent a relevant source of sST2 in HF patients and concentrations of sST2 in pulmonary oedema from individuals with HF strongly correlate to blood values. This link to pulmonary pathophysiology may explain why sST2 correlates with the presence and severity of pulmonary congestion in HF. This contrasts with NPs, which are also upregulated in HF and correlate

with pulmonary congestion but are only expressed in cardiomyocytes and not the lungs. For this reason, an additional role of sST2 relative to NPs for evaluating the HF phenotype and prognosis seems likely from a biological perspective [10].

The IL-33/ST2L axis is mainly a signalling mechanism of the immune system but also has anti-apoptotic, anti-fibrotic and anti-hypertrophic effects in the heart. sST2 acts as a decoy receptor for IL-33, thus blocking these positive effects. [11]. IL-33 is an interleukin-1-like cytokine secreted by living cells in response to cell damage. IL-33 functions as a danger signal or an alarm by signalling the presence of tissue damage to local immune cells after exposure to pathogens, injury-induced stress, or death by necrosis [3]. Once secreted, IL-33 binds the ST2L receptor, and IL-33/ST2L signalling leads to inflammatory gene transcription and ultimately to the production of inflammatory cytokines/chemokines and an immune response [5,6]. sST2 avidly binds to IL-33 in competition with ST2L, thus functioning as a decoy receptor for IL-33. Therefore, the interaction of sST2 with IL-33 blocks the IL-33/ST2L system [12].

Tumour necrosis factor alpha (TNF α), on the other hand, is an inflammatory cytokine from the TNF ligand superfamily produced by macrophages, monocytes or many other cells during acute inflammation. Their primary role is intracellularly signalling various events, causing necrosis or apoptosis [13]. It was initially understood as an anti-tumour and cytotoxic ligand, as its effect on the necrotic regression of tumours was observed [14,15]. Bacterial lipopolysaccharide has long been considered one of the most important triggers for TNF α production [16]. Yet now it is known that a wide range of stimulation can cause TNF α production in their respective cells – including viral, parasitic, mycotic antigens, enterotoxins, complement proteins, immune complexes,

interleukin (IL)-1, interferons and TNF α itself (through autocrine stimulation)[17]. With a wide array of activating mechanisms, it is helpful to note that TNF α biosynthesis is suppressed by IL-4 and other ligands that lower the concentration of cyclic adenosine monophosphate [14]. Furthermore, it is not stored intracellularly, and de novo synthesis can be stimulated through various triggers. On the contrary, TNF α as a cytokine can stimulate the release of some anti-inflammatory factors, such as IL-10, endogenous corticosteroids and prostanoids, that negatively regulate its expression and bring inflammation to a halt. All things considered, TNF α is necessary for the communication between resident cells in various systems and the cells of the immune system – its primary role is controlling the immune response and inhibiting its severity and duration [15].

TNF α induces intracellular signalling events due to its binding to one of two cell membrane-bound TNF-receptors (TNFR) – TNFR1 and TNFR2. Both are transmembrane glycoproteins, yet they are different in their locations. TNFR1 is highly common and expressed in every cell type in the human organism, while TNFR2 is limited to immune and nervous system cells and the endothelium [18]. The interesting part is what happens further inwards, as TNF binds to TNFR. TNFR1 has an associated death domain (TRADD) – an adapter molecule that starts the cascade for interactions with different kinases – this pathway is exactly what commits the involved cell to apoptosis [18]. In addition, other pathways are stimulated, inducing the production of adhesion molecules and chemokines, promoting the attachment of inflammatory cells to the vascular walls and their activation, as well as chemotaxis [19].

Both sST2 and TNF α have a vital role in the signalling pathways of the immune system. sST2, belonging to the IL-1 family, has earned its

reputation as an essential signalling cytokine, with the IL-33/ST2L signalling axis also showing anti-apoptotic, anti-fibrotic and anti-hypertrophic effects on the cardiac myocytes. On the other hand, TNF α , as one of many TNF ligands, works to signal, mediate and stimulate or halt immune responses with a pathway through its TRADD domain that each cell type possesses in their TNFR1 receptor responsible for inducing cell apoptosis. With their biological and physiological standings analysed, both cytokines have an essential role in the pathogenesis of heart failure, and with it – practical usability in determining the phenotype and prognosis seems likely.

1.3. Inflammation And The Pathogenesis Of Heart Failure

The article proving the correlation between increased circulatory levels of TNF α and heart failure with reduced ejection fraction (HFrEF) was first published in 1990 [20]. It provided the earliest evidence to the understanding cardiology still leans on while explaining the pathophysiology of heart failure – patients with chronic heart failure experience constant, ongoing inflammation. This has paved the way for multiple subsequent clinical and experimental studies. One thing seemed inevitable – in both acute and chronic heart failure, activation of the innate and adaptive immune systems plays an important role, so subsequently, theories of utility in therapeutically targeting the inflammatory response have also surfaced. However, this new pathway for finding new treatments faced disappointment in stage III of clinical trials, and researchers started doubting that the initial theory of inflammation has a crucial role in the pathogenesis of heart failure [21–23]. Could inflammation be the consequence and not the cause of heart failure?

During myocarditis or other types of injury (ischemia or volumetric hemodynamic overload), innate and adaptive immune systems get activated. Innate immunity works through a general, nonspecific response, while the adaptive system is specific through signalling and mediation provided by B and T cells. After an injury to the myocardium, the general inflammation provided by the innate immune system ensures a cytoprotective response that ensures a short-term adaptation to the stressor [22]. If this response becomes unregulated and acute inflammation becomes chronic, it leads to left ventricular (LV) dysfunction and remodelling – the basis of HFrEF.

This innate immune system response activation starts with transmembrane and cytosolic pattern recognition receptors (PRRs) that bind to pathogen-associated molecular patterns (PAMPs) and endogenous material from damaged and apoptotic or necrotic cells (damage-associated molecular patterns – DAMPs). These receptors are expressed in various heart tissues, including cardiomyocytes, tissue-resident immune cells, and endothelial cells. Activating these PRRs results in biochemical pathways that regulate gene expression, including ones that encode pro-inflammatory cytokines and chemokines [24].

Transcriptional profiling of human cardiac samples showed that hearts with the expressed failure phenotype and ones without it differ in the expression profiles of genes related to this innate immune response [25].

Currently, two evidence pathways prove that inflammation in the myocardium is chronically present in individuals with both ischemic and non-ischemic heart failure. The first one is important to this article – the presence of TNF α and IL-1 β with chemokines in patients with both ischemic and dilated cardiomyopathy, but not in patients proven not to have heart failure [26]. The second evidence

line leads to naive and activated T lymphocytes, macrophages and NK cells being observed in histological specimens of patients with chronic heart failure, both ischemic and non-ischemic. Yet, the heart samples that were chosen for this study were selected from patients with the absence of fresh myocardial injury of any kind, viral or bacterial infection and immunological abnormalities – which proves that the presence of immune cells is associated with heart failure itself and leads to the idea that the degree of chronic inflammation in the myocardium might be functionally significant [27]. So far, the non-cellular components of chronic inflammation (such as TNF α , IL-1 β , IL-6 and others) have been shown to exert adverse inotropic effects on isolated, contracting cardiomyocytes in vitro, in intact animal hearts ex vivo and in vivo in animal studies [28–31]. Studies that employed prolonged pro-inflammatory signalling were performed, and, for example, TNF was infused into the peritoneal cavity of rats at concentrations like those in patients with heart failure, resulting in changes to LV dimensions and function that became more pronounced over time [32]. Other studies also showed that mice overexpression of the TNF gene developed progressive LV dilatation. With that, it was demonstrated that TNF activates specific metalloproteinases that degrade extracellular collagen matrix and, as a result – promote LV dilatation [33].

Even with the role of inflammation in the pathogenesis of heart failure, if not fully understood, then at least explored enough to provide food for thought of using it in prognosis or treatment, it is crucial to learn from the previous failed stage III clinical trials. Furthermore, the promising results of the CANTOS trial show that inflammatory biomarkers can be used to identify patients who would benefit from an anti-inflammatory treatment strategy [34]. Other inflammatory biomarkers (such

as sST2 and others) are perceived as applicable for future further selection of patients for clinical anti-inflammatory therapy trials. Another potential strategy for a multi-biomarker approach could be identifying patients with heart failure, in whom chronic inflammation is associated with further myocardial damage, as opposed to patients in whom this immune response acts purely as a homeostatic effort for dealing with hemodynamic triggers [27]. Chronic inflammation, in general, plays a vital role in the pathogenesis of heart failure. Both innate and adaptive immune systems have been proven to participate in response to a wide array of myocardial damage. Yet, their malfunction, which results in chronic, uncontrolled inflammation, is something research still does not seem to have a complete biological picture of. Biomarkers, as avid participants in the immune response, might provide some light and utility not only in further research on the role and pathways of chronic inflammation but, predictably – in classifying patients according to the physiology of their ailment and consequently - in studies and trials on the prognosis and maybe even anti-inflammatory treatment for patients with heart failure.

1.4. Comparison With Already Established Biomarkers. Clinical Value

An ideal biomarker in HF should be (1) measured non-invasively and at low cost, (2) highly sensitive to allow for the early detection of the disease, (3) unaffected or minimally affected by comorbid conditions, and (4) responsive to treatment effects [2]. Well used biomarkers are crucial in ensuring precise treatment and risk management [35]. The most established biomarkers in HF are B-type natriuretic peptide (BNP) and its co-secreted amino-terminal pro-peptide fragment (NT-proBNP), which reflect cardiac transmural wall stress. BNP's are strong predictors of HF presence and severity and

provide prognostic information [36]; therefore, BNP and NT-proBNP have a class 1 recommendation in the current European Society of Cardiology (ESC) and American College of Cardiology/American Heart Association (ACC/AHA) HF guidelines for these indications [3,4]. With that, BNP and NT-proBNP continue to receive attention from the ESC and other expert organisations in regards to their diagnostic value and therefore will keep their features in clinical recommendations [37].

Beyond their well-established diagnostic role in acute and chronic settings, the role of BNP and NT-proBNP in risk stratification is gaining more momentum in clinical practice. Low values of NPs at discharge reflect the achievement of greater decongestion, which correlates with a lower risk of re-hospitalization and death. In addition, the pre-discharge value can be used to determine the intensity of monitoring and the timing for follow-up visits [5].

However, there are significant limitations to natriuretic peptide (NP) testing in HF. Most important is the impact caused by conditions commonly associated with HF, such as atrial fibrillation (AF), kidney dysfunction and obesity, as well as a wide range of cardiac and non-cardiac abnormalities associated with an increase in parietal tension without necessarily being linked to fluid retention. NP concentrations also vary substantially with age and sex, which introduces difficulties in using thresholds for decision-making. Beyond these issues, the concentrations of BNP and NT-proBNP only reflect one aspect of the considerably complex pathophysiology of HF. Accordingly, a broader palette of biomarkers would be expected to provide an essential depth of understanding of individuals affected by the diagnosis. One of those would be soluble ST2 (sST2), which was first classified as an indicator of ventricular myocyte stress but is mainly produced in extracardiac tissues in response to

inflammatory and fibrotic stimuli, representing an indicator of the myocardial fibrotic process and a predictor of cardiac remodelling [9].

Regarding sST2, it is crucial to remember its nonspecific nature, resulting in utility limitations and rendering it unusable for heart failure diagnostics. Yet, it has been proven helpful in risk management. A meta-analysis performed with 4835 patients diagnosed with acute HF discovered that both discharge and admission sST2 values were accurate in predicting all-cause (HR 2.46 [1.80–3.37] and 2.06 [1.37–3.11], respectively), and CVD related mortality (HR 2.29 [1.41–3.73] and 2.20 [1.48–3.25], respectively)– furthermore, discharge sST2 values predicted rehospitalisation for HF patients (HR 1.54 [1.03–2.32]) [38]. A 150-patient study has also helped predict 3-month mortality during a hospital stay regardless of BNP or NT-proBNP [39]. The Translational Initiative on Unique and Novel Strategies for Management of Patients with Heart Failure (TRIUMPH) conducted a cohort study on 496 patients with acute HF and performed seven separate measurements in 1 year. Similar results were shown – baseline sST2 showed a reliable prediction of all-cause or CVD-related death or HF-related hospitalisation (HR for each standard deviation increase of $\log_2(\text{ST2})$: 1.30 [1.08–1.56]). Meanwhile, the regularly repeated tests proved even more valuable – the changes across measurements were more reliable for predictions (HR for each standard deviation increase of the $\log_2(\text{ST2})$: 1.85 [1.02–3.33]) independently from NT-proBNP [40]. sST2 and its independency from high-sensitivity troponin-T (hs-TnT) and NT-proBNP and the prognostic value have been pointed out [41]. Furthermore, the fact that sST2 is less influenced by age than the two biomarkers, as mentioned earlier, is also prominent in studies [42].

With all the evidence in mind, it is worth mentioning that sST2 has been prevalent in ACC/AHA

guidelines for quite some time. They recommend its measurement for evaluating the prognosis of patients with chronic HF (recommendation class IIb, B level of evidence) [43]. Meanwhile, ESC guidelines are more cautious and mention a lack of evidence as the explanation for not recommending the usage of sST2 measurements in clinical practice [4].

As for TNF α – the same issues as with sST2 arise, non-specificity being one of the main ones. Especially with its prominence in autoimmune and rheumatic diseases, the utility of the TNF α titres appears slim. Still - a study with 60 patients was conducted, tracking various established and experimental biomarkers and their relation to CVD-related mortality. They found a significant correlation between raised TNF α titres and lowered left ventricle ejection fraction (LVEF) (mean LVEF value was around 22%), as well as between TNF α titres and NYHA classes (55% of patients with abnormal values were in NYHA class IV) [44]. It is worth mentioning that TNF, the possible cardioprotective effects and TNF α receptors, by their right, are mentioned in a fair number of articles as a potential target for pharmacological treatment. However, this is out of the scope of this study; for further reading, please refer to [45]. Various studies have been conducted and show a broad scope of significant relation between the negative inotropic phenotype of heart failure and TNF α [46]. Yet, with progress reports, it seems like TNF α and its primary utility will continue to treat and manage illness and complications rather than diagnostics and risk evaluation, making these aspects incomparable to established and new cardiac biomarkers.

New studies have shown even more new biomarkers, that are worth scientific attention – for example, BMP10, which has shown potential in acute dyspnea studies[47]. The evidence and, consequently, agreements are straying towards

acknowledging both the triumphs and downfalls of already established biomarkers such as BNP, NT-proBNP or hs-TnT, yet also leaning towards multi-biomarker approach as the safest middle ground for the management of HF [48]. This tactic has already started to appear vaguely in recommendations as new biomarkers are taking their place next to the tried and tested ones, even though the evidence is still lacking for it to be entirely trustworthy and make its way into day-to-day practice [43]. Yet, the chances for a multi-biomarker approach to make it in time are positively hopeful, already by the biophysical properties of the markers and by the studies that are already testing their value, showing significant chances of lowering HF-related morbidity and mortality if evaluated, prepared, proven and placed among what we already know.

3. Results

Recent literature highlights NT-proBNP as a cornerstone in the diagnosis and management of heart failure, with strong support from international guidelines. Emerging biomarkers such as soluble ST2 (sST2) and tumor necrosis factor-alpha (TNF- α) provide additional prognostic value, particularly in identifying inflammatory activity and myocardial stress. The integration of these biomarkers into clinical algorithms improves diagnostic precision and supports individualized treatment strategies.

4. Discussion

Therapeutic translation is challenging, particularly in complex conditions like heart failure. Research indicates that using sST2 alongside NT-proBNP enhances prediction accuracy for adverse outcomes, but this approach is not comprehensive. It is essential to grasp the mechanisms behind sST2 synthesis and the binding assay sites. Clinicians require clarity on when to measure sST2 levels and how this information can enhance patient care. In

acute heart failure, checking sST2 levels upon admission and discharge is advisable. Failure to see a decrease in these levels may indicate heightened risks for patients, such as extended hospital stays, more rapid adjustments to heart failure medications after stabilisation, and rigorous monitoring for pulmonary congestion. In cases of chronic heart failure, sST2 levels can indicate outcomes and the potential for reverse remodelling when treatments are followed consistently. Assessing sST2 is vital for risk stratification and can be considered alongside natriuretic peptides and troponins; however, more research is needed to confirm its role in directing treatment choices, like altering medications or referrals for defibrillator placement. Although TNF α is less specific to cardiac stress than sST2, it reflects systemic inflammation in heart failure patients. While combining TNF α with cardiac-specific biomarkers could enhance risk prediction, its value as an independent prognostic factor remains uncertain. Combining these biomarkers may yield a more comprehensive evaluation of heart failure severity, considering cardiac-specific and systemic inflammatory responses. This multimarker strategy should aid in better risk categorisation and enable more tailored treatment options.

5. Clinical Perspectives

Biomarkers play a crucial role in the modern clinical management of heart failure. NT-proBNP remains the most reliable and widely recommended marker for diagnosing heart failure, particularly in patients presenting with nonspecific symptoms such as dyspnea. Emerging biomarkers, including soluble ST2 (sST2) and tumor necrosis factor-alpha (TNF- α), offer additional prognostic information by reflecting myocardial stress and inflammatory activity. While their routine use in clinical practice is still evolving, they may prove valuable in identifying high-risk patients and tailoring therapy.

The integration of biomarkers into clinical algorithms enhances diagnostic accuracy, supports early intervention, and enables a more individualized approach to treatment. Ongoing research and guideline updates will further clarify the role of these emerging markers in everyday practice.

6. Conclusions

Biomarkers such as NT-proBNP have a well-established role in the diagnosis, risk stratification, and management of heart failure, as confirmed by recent guidelines and expert consensus. Emerging markers like sST2 and TNF- α offer additional insights into disease severity, inflammation, and prognosis, although their routine clinical use is still being defined. While biomarker-guided strategies are shaping a more precise approach to heart failure care, further studies are needed to fully integrate novel biomarkers into standardized clinical practice. Their careful application can enhance diagnostic accuracy, support earlier intervention, and contribute to more personalized treatment pathways.

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