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Prognostication of heart failure development and advance: the role of high-sensitive ST2

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Abstract

Currently the care of patients with heart failure (HF) may base on clinical- and biomarker-guided therapy. Natriuretic peptides, high-sensitive cardiac troponins, galectin-3 were recognized to the evolution and outcome of cardiac diseases. Recently trials have shown that circulating level of soluble ST2 (sST2) measured at pre-discharge might have predictive value in short-term outcomes and probably long-term mortality among subjects with acute and chronic HF. Although preliminary results of clinical studies on this novel biomarker are encouraging, its role in the risk stratification in HF is needed to establish. The short comment reports that the prognostic performance of elevated sST2 with respect to cardiovascular (CV) mortality and newly diagnosed HF in general patient population is currently limited to a number of modest-quality studies and is required to be assessed in large comprehensive trials. The predictive value of sST2 appears to be superior compared with BNP and similar to galectin-3 among subjects with none-CV diseases is discussed. The role of elevated sST2 level as independent predictor of outcomes in HF population is considered.

Abbreviations: BNP: brain natriuretic peptide; CV: cardiovascular; HF: heart failure; IL: interleukin; NYHA : New york heart association

Heart failure (HF) remains a leading cause of cardiovascular (CV) mortality worldwide [1]. Over the past decades, the clinical use of multiple biomarkers has changed diagnostic and management of CV disease [2]. Current clinical guidelines have recommended to use single and serial biomarker measurements for diagnostic purpose, risk stratification and guided-therapy of patients with acute and chronic HF [3,4]. Natriuretic peptides, high-sensitive cardiac troponins, galectin-3 were recognized to the evolution and outcome of cardiac diseases [5-7]. Recently trials have shown that circulating level of soluble ST2 (sST2) measured at pre-discharge might have predictive value in short-term outcomes and probably long-term mortality among subjects with acute and chronic HF [8-10]. Although preliminary results of clinical studies on this novel biomarker are encouraging, its role in the risk stratification in HF is needed to establish.

sST2 is a member of interleukin-1 receptor family that is secreted from cardiomyocytes and cardiac fibroblasts due to biomechanical stress and volume overload [11]. ST2 is expressed on Th2 cells and may regulate Th2 responses mediating inflammation and appears to act as a decoy receptor for IL-33 [12]. Overall sST2 is considered a biomarker of ventricular fibrosis, remodeling and inflammation [9].

Although concentration of sST2 correlates well with brain natriuretic peptide (BNP) levels in HF patients, in fact, circulating sST2 levels were not significantly changed according to the degree of renal dysfunction [13,14]. This fact was considered an advantage of sST2 compared with other markers of biomechanical stress (natriuretic peptides), inflammation (galectin-3) and myocardial injury (cardiac specific troponins) in HF individuals. It has been postulated that sST2 added to other biomarkers might improve multiple biomarker strategy for risk stratification of death in a real-life HF and increase efficacy of biomarker-guided care based on BNP measurements in combination with established HF mortality risk factors (age, sex, left ventricular ejection fraction, NYHA class, ischemic HF etiology, diabetes, estimated glomerular filtration rate, sodium level, hemoglobin level) [15,16]. Unfortunately, elevation of sST2 in circulation is not specific for HF and has not a powerful diagnostic effect on presentation of cardiac dysfunction unless reduced left ventricular ejection fraction [17,18]. In this context, there are prompts regarding use of sST2 in combination with other inflammatory biomarkers, i.e. galectin-3, and growth-differentiation factor-15, to increase sensitivity and specificity of multiple biomarker models in diagnostic of HF including asymptomatic stage and HF with preserved left ventricular ejection fraction [19,20]. As a result of similar approach, we have a large body of evidence regarding extending prognostication value of sST2 added to cardiac biomarkers, such as BNP, in none cardiovascular patients [21-23]. Inversely, in a healthy general population from Finland, sST2 did not improve long-term prediction of cardiovascular events including heart failure or all-cause mortality [24]. Thus, sST2 appears to not be able to identify individuals with elevated CV risk and add to existing CV risk prediction algorithms.

In conclusion, the diagnostic capacities of sST2 to identify HF due to lower specificity compared BNP is not discussed, although utility sST2 incorporated into multiple biomarker models in diagnostic of HF, especially in patients with kidney dysfunction, diabetes, older age, is mentioned attractive. The prognostic performance of elevated sST2 with respect to CV mortality and newly diagnosed HF in general

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patient population is currently limited to a number of modest-quality studies and is required to be assessed in large comprehensive trials. The predictive value of sST2 appears to be superior compared with BNP and similar to galectin-3 among subjects with none-CV diseases. However, in spite of the fact that elevated sST2 level has found an independent predictor of clinical outcomes in HF population, its role in the guided management of HF patients is still not clear. Overall, larger randomized clinical trials are necessary to assess the value of peak concentration and serial measurements of sST2 in HF to improve prediction of outcomes and management.

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