Soluble ST2 for Prognosis and Monitoring in Heart Failure

The New Gold Standard?

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Biomarkers have emerged as indispensable tools for diagnosis, prognosis, and monitoring in a variety of cardiovascular diseases, and several are part of the standard of care. In particular, natriuretic peptides (NPs) have evolved over the past 15 years to become part of routine care for heart failure (HF) diagnoses (rule-in and rule-out), in both acute and ambulatory settings (1,2). The prognostic value of NPs is also well established (3), but adoption by clinicians has been irregular. Some nuances related to NP levels in elderly patients, patients with renal failure, and those with a high body mass index (BMI) have generated noise that nonexperts have found difficult to handle. NP monitoring and therapy guidance have been investigated in multiple randomized prospective clinical trials to date, but results have been conflicting; thus, the field remains somewhat orphaned and filled with uncertainties (4). Despite the well-documented successes and strengths of NPs, there is ample room for improvement in the way we risk-stratify patients with HF. Although a large number of candidate biomarkers have been evaluated to help fill this gap, few have survived the rigorous studies that are prerequisite to translation into the clinical realm.

ST2 PATHOBIOLOGY

A comprehensive review of the complex interleukin (IL)-33/ST2 pathway is beyond the scope of this editorial and may be found elsewhere (6). Briefly, ST2 is a member of the IL-1 family of proteins. Through alternative splicing, ST2 is found in multiple isoforms, including a transmembrane form (ST2 ligand, or ST2L) and a soluble, circulating form (ST2) (6). In

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the nonfailing heart, IL-33, produced by cardiac fibroblasts, binds to ST2L, and this complex activates a number of intracellular signaling cascades. This signaling ultimately leads to nuclear factor (NF)-κB upregulation and the prevention of fibrosis and hypertrophy. In HF, soluble ST2, the isoform measured in current assays, is thought to act as a decoy receptor for IL-33. The presence of high ST2 concentration blocks the favorable effects of IL-33 by abrogating activation of the cascade triggered by the IL-33/ST2L interaction. Consequently, higher soluble ST2 is associated with increased myocardial fibrosis, adverse cardiac remodeling, and worse cardiovascular outcomes (7,8) (Figure 1).

### ST2 AND PROGNOSIS IN HF

Most studies conducted to date that focused on the prognostic value of HF biomarkers have related a single baseline measurement to adverse outcomes during follow-up. Single ST2 measurements have consistently been shown to have prognostic and predictive value. These properties were recently confirmed in 2 comprehensive meta-analyses conducted on chronic and acute HF (9,10). In chronic HF, ST2 was related to a hazard ratio (HR) of 1.75 for all-cause death and 1.79 for cardiovascular (CV) death (8). In acute HF, admission ST2 had an HR of 2.29, and discharge ST2 had an HR of 2.20 for CV death. Moreover, discharge ST2, but not admission ST2, was predictive of HF rehospitalization during follow-up (9).

A recently developed HF risk calculator, the Barcelona bioHF calculator (available online) incorporates ST2 (together with N-terminal pro-B-type natriuretic peptide [NT-proBNP] and high-sensitivity troponin T [hs-TnT]) to calculate the risk of death and/or HF hospitalization within 5 years. This is a Web-based calculator that refines risk-stratification and allows rapid, easy, interactive calculations of prognosis and life expectancy at the individual patient level (11). Further, as expected in a fibrosis biomarker, ST2 also provided prediction of sudden death in a nested case-control study of ambulatory patients with HF and reduced ejection fraction (12). A clinical and biomarker score, the ST2-R2 score, has been developed to predict relevant reverse remodeling. This score contains ST2 and 5 clinical variables,
including nonischemic etiology, left bundle branch block, HF duration, baseline left ventricular ejection fraction, and beta blocker treatment (13). This ST2-R2 score has provided proof-of-concept that the addition of ST2 to several other clinical parameters significantly improved their reverse remodeling predictive accuracy. The other biomarkers evaluated, NT-proBNP, hs-TnT, and galectin-3, did not provide reverse remodeling added value.

**ST2 MONITORING IN HF**

Repeated ST2 measurements more accurately reflect the dynamic and progressive course of HF compared to a single measurement. Furthermore, the low coefficient of variation in ST2 concentrations gives ST2 a potential advantage for serial testing in patients with HF over other more established biomarkers (i.e., NPs). Moreover, circulating ST2 is not substantially affected by renal dysfunction or BMI. Boisot et al. (14) showed that, among patients hospitalized with acute HF, failure of ST2 to drop by at least 15% over the course of hospitalization was associated with an increased risk of death at 90 days (14). Bayés-Genís et al. (15) built upon this concept by measuring ST2 2 weeks apart in a cohort of outpatients with decompensated HF. They observed that these patients were at increased risk of adverse outcomes when ST2 failed to drop by at least 25% (15). Other studies in patients hospitalized with HF showed that the so-called “ST2 nonresponders,” or individuals with decompensated HF that failed to show an adequate drop in ST2, were at increased risk of poor outcomes (16). More recently, the PROTECT (Pro-B-type natriuretic peptide outpatient-tailored chronic heart failure therapy) study, which included patients with chronic HF and reduced ejection fraction, measured the percent of time with ST2 below the 35 ng/ml cutoff level (or “time in ST2 response”). They found that greater times in ST2 response predicted lower risk of adverse events (17).

In this issue of the Journal, van Vark et al. (5) examined the predictive value of frequently measured ST2 in a population with acute HF. The study design and the findings reported, in addition to providing pathophysiological insight, have the potential to change current clinical practices. A number of issues merit particular attention. First, up to 7 ST2 measurements were planned during a 1-year follow-up. During hospitalization ST2 was measured 3 times, and at outpatient follow-up visits ST2 was assessed 4 more times at pre-defined time points. This study clearly shows that baseline ST2, and even more, repeated ST2 measurements represent a strong, independent predictor of the composite endpoint of all-cause mortality or readmission for HF during a 1-year follow-up in patients admitted with acute HF. HF is a dynamic and often progressive disease in which inflammation, cardiac fibrosis, and remodeling are ongoing processes that cannot be captured in a single biomarker assessment at 1 point in time. Consequently, the dynamic changes in ST2 during follow-up provided predictive value. Second, ST2 concentrations increased in patients before reaching the primary endpoint (the so-called “U-shape” ST2 pattern), whereas ST2 stabilized in patients without the primary endpoint during follow-up (the so-called “1-shape” ST2 pattern). Indeed, almost twice as many patients who reached the primary endpoint during follow-up exhibited a U-shaped ST2 pattern. Finally, another finding from the study by van Vark et al. (5) was that repeated ST2 conferred additional, independent prognostic information to that offered by baseline and repeated NT-proBNP. This observation may be explained by the fact that NT-proBNP and ST2 reflect different underlying pathophysiological processes in HF.

Collectively, current evidence suggests that ST2 may be regarded as the new gold standard biomarker for prognosis and monitoring in HF. Further, the value of ST2 in clinical decision-making has also been examined. In patients with post-infarction ventricular dysfunction, a post hoc analysis from the EPHECUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival) trial showed that patients with low ST2 had less adverse left ventricular remodeling, regardless of the treatment arm (18). In patients with chronic HF, ST2 dropped for each upward titration of the β-blocker dose; the absolute benefit of high β-blocker doses was greatest in patients with ST2 >35 ng/ml (19). These studies provide a roadmap for future clinical trials of ST2-guided therapy.

Based on the strength of evidence, we argue the time is right for investigators to perform well-designed, prospective, international, multicenter trials of ST2-guided HF care to obtain actionable data in a timely fashion. It is imperative to avoid the mistakes made in NP-guided trials: multiple small, underpowered studies with variable endpoints is the wrong way to spend limited research resources, and an approach that may slow the move toward CV precision medicine.

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