Soluble ST2: A Novel Prognostic Biomarker of Heart Failure

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ST2, otherwise known as suppression of tumorigenicity 2 and,a member of the interleukin-1 (IL-1) receptor family, consists of a trans-membrane ligand (ST2L) and a soluble form (sST2). ST2 is released while cardiomyocytes and cardiac fibroblasts are undergoing biomechanical strain,[1,2] and has been identified as a novel marker of cardiac stress, fibrosis and remodeling.[3-6] IL-33, a functional ligand of ST2L,[7,8] exerts antihypertrophic and antifibrotic effects on myocardium by inhibiting the actions of phenylephrine and angiotensin II.[2] Additionally, soluble ST2 acts as a decoy receptor of IL-33 and attenuates its cardioprotective properties.[2] Previous studies have demonstrated the role of ST2 in predicting hospitalization and mortality in heart failure, independent of natriuretic peptides and other clinical variables.[9-17] In 2011, the U.S. Food and Drug Administration (FDA) delared the Presage® ST2 Assay (Critical Diagnostics, San Diego, California, USA), which is typically used in conjunction with clinical evaluation as an aid in assessing the prognosis of patients diagnosed with chronic heart failure.

A recent study in Taiwan showed ST2 measurements offered a diagnostic benefit for hypertensive patients with stable heart failure and normal ejection fraction.[18] In a pilot study on ST2 concentration and renal function in heart failure, the prognostic value of ST2 was not affected by renal function and was even improved in patients with renal insufficiency compared with the total study cohort.[19] Serial monitoring of ST2 concentrations in patients with decompensated heart failure also predicts mortality. In a study of 150 patients with acute decompensated heart failure, Boisot et al. reported that patients with ≧ 15.5% decrease in ST2 levels during the hospital stay had a lower 90-day mortality than those with < 15.5% decrease (7% vs. 33%).[20] Using an enzyme-linked immunosorbent assay (Medical & Biological Laboratories Co., Woburn, MA, USA), they found that the two groups did not differ in baseline ST2 levels, but the levels in the death group were elevated significantly in subsequent samplings. They concluded that the percentage change in ST2 concentrations during acute HF treatment was predictive of 90-day mortality independent of natriuretic peptide levels.

It is well-established that the B-type natriuretic peptide (BNP) and NT-proBNP have been used for differentiating causes of dyspnea, predicating prognosis, and guiding management of heart failure. Table 1 lists the

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Table 1. FDA indications of BNP, NT-proBNP and ST2

	BNP	NT-proBNP	ST2
FDA indication	Triage® BNP Test (Biosite Diagnostics, San Diego, CA): 1. Diagnosis and assessment of severity of congestive heart failure 2. Risk stratification of acute coronary syndrome	Elecsys® proBNP assay (Roche, Indianapolis, IN): 1. Diagnosis of congestive heart failure. 2. Risk stratification of acute coronary syndrome and congestive heart failure.	Presage® ST2 Assay (Critical Diagnostics, San Diego, CA): 1. In conjunction with clinical evaluation as an aid in assessing the prognosis of chronic heart failure.

BNP, B-type natriuretic peptide; FDA, Food and Drug Administration; NT-proBNP, N-terminal of the prohormone brain natriuretic peptide.

FDA indications of BNP, NT-proBNP and ST2. In combination with natriuretic peptides, ST2 measurements provide incremental diagnostic and prognostic values in patients with heart failure (Table 2-4).[9,21,22] Therefore, incorporation of ST2 with natriuretic peptides and other clinical variables in a multi-maker model will be beneficial in risk stratification, prognosis predication and guiding heart failure treatment. A risk stratification calculator (the Barcelona Bio-Heart Failure Calculator: www.bcnbiohfcalculator.cat) using clinical variables plus ST2, NT-proBNP and hsTnT has recently been developed for individual patient prediction.[17]

Table 2. Hazard ratios of death or heart transplant in patients with heart failure[9,*]

	ST2 ≤ 35 ng/ml	ST2 > 35 ng/ml
NT-proBNP ≤ median	1	2.3
NT-proBNP > median	2.7	10

[a] At a median follow-up of 2.8 years. NT-proBNP, N-terminal of the prohormone brain natriuretic peptide.

Table 3. One-year mortality rate in patients with acute heart failure[21]

	ST2 ≤ median	ST2 > median
NT-proBNP ≤ median	10%	40%
NT-proBNP > median	28%	56%

NT-proBNP, N-terminal of the prohormone brain natriuretic peptide.

Table 4. One-year cardiac event rate in patients with decompensated heart failure[22]

	ST2 ratio[b] ≤ 0.75	ST2 ratio > 0.75
NT-proBNP[c] ≤ 1,000 pg/mL	0%	45%
NT-proBNP > 1,000 pg/mL	45%	72%

[a] Cardiac events: heart failure admission, heart transplantation, or death. [b] ST2 ratio: ST2 at 2 weeks after initial outpatient visit divided by ST2 at initial visit. [c] NT-proBNP: measured 2 weeks after initial visit. NT-proBNP, N-terminal of the prohormone brain natriuretic peptide.

NO CONFLICT OF INTEREST

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