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# ST2: A Novel Remodeling Biomarker in Acute and Chronic Heart Failure

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**Abstract** ST2, a member of the interleukin-1 receptor family, is a novel biomarker of mechanical stress measurable in serum that has been shown in animal and in vitro models to be physiologically linked to cardiac hypertrophy, fibrosis, and ventricular dysfunction. In patients with acute myocardial infarction and heart failure (HF), an elevated serum level of the soluble isoform of ST2 is associated with an increased risk of mortality or future HF, independent of natriuretic peptides, and correlates with markers of ventricular structure and function. In acute HF, elevated soluble ST2 levels strongly associate with the presence and severity of the disease and forecast short- and long-term mortality independent of other traditional clinical, biochemical, and echocardiographic markers of risk. This review discusses the biology and physiology of ST2, as well as its implications on the pathogenesis and prognosis of patients with acute coronary syndromes or acute and chronic HF syndromes.

**Keywords** Heart failure · Remodeling · Prognosis · Biomarker

## Introduction

In patients with acute heart failure (HF), elevated filling pressures and ventricular dysfunction contribute to increased wall stress and promote the release of natriuretic peptides (eg, B-type natriuretic peptide [BNP] and its amino-terminal cleavage fragment, N-terminal prohormone BMP [NT-proBNP]). Induced by pressure or volume overload [1, 2], BNP and NT-proBNP are related to the severity of abnormalities in cardiac structure and function, such as poorer ventricular systolic and diastolic function, chamber dilatation, valvular heart disease, and pulmonary hypertension [3, 4]. Even when considered in the presence of comprehensive echocardiographic data in adjusted models, natriuretic peptides remain powerfully prognostic for long-term mortality and readmission for HF [5, 6].

Looking beyond the natriuretic peptides, increasing interest has been given to a class of markers that predict deleterious processes subsequent to wall stretch, namely ventricular remodeling. Included among these markers is ST2.

A member of the interleukin (IL)-1 receptor family, ST2 is a biomarker of mechanical stress, upregulated in isolated cardiomyocytes exposed to mechanical strain [7], and derangement of ST2 signaling leads to a phenotype quite consistent with myocardial remodeling. As would be expected, therefore, in patients with acute myocardial infarction, elevated soluble ST2 (sST2) levels are associated with an increased risk of mortality or HF, independent of natriuretic peptides [8, 9], whereas serial alterations in sST2 level over time predict outcomes independent of natriuretic peptides [10]. Furthermore, in patients with HF, sST2 levels strongly associate with the severity of heart failure and forecast 1-year mortality additive to NT-proBNP [11-13].

This review discusses the biology and physiology of ST2, specifically its implications on the pathogenesis and prognosis of patients across the spectrum of American Heart Association (AHA) HF Stages, such as those with acute coronary syndromes or acute and chronic HF syndromes.

## Molecular Biology of ST2

A member of the IL-1 receptor family, ST2 was initially described by Weinberg et al. [7], found in a screen of gene

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transcripts expressed by mechanically stressed cardiomyocytes in an in vitro model [7]. Because of alternative splicing and 3' processing at the RNA level, ST2 is expressed in a transmembrane form (ST2 ligand [ST2L]) as well as in a soluble, circulating form (sST2) [14]. Both sST2 and ST2L are induced in cardiomyocytes and fibroblasts exposed to biomechanical stress [7]; ST2L is thought to be involved in modifying immunologic processes, specifically T helper 2–mediated responses [15].

Recently, IL-33 has been identified as the ligand for ST2, providing a potential mechanism for ST2 in the pathogenesis of HF [16••]. In an in vitro model of rat cardiomyocyte stretch, Weinberg et al. [7] demonstrated a direct relationship between duration of biomechanical strain and IL-33 and ST2 expression. Furthermore, administration of sST2 to rat myocytes cultured with IL-33 blocked the prohypertrophic influence of IL-33 in a dose-dependent fashion, suggesting that soluble ST2 may serve as a "decoy receptor" for circulating IL-33.

In an in vivo model of pressure overload, endomyocardial biopsies from mice deficient in ST2 demonstrated a greater degree of myocyte hypertrophy and fibrosis and poorer fractional shortening than wild-type mice after 4 weeks of transaortic constriction. Although IL-33 rescued the hypertrophic phenotype in wild-type mice, it was unable to attenuate cardiac hypertrophy and fibrosis in ST2-deficient mice, suggesting that IL-33/ST2 signaling may protect against adverse cardiac remodeling in vivo. Moreover, cardiomyocytes from ST2-deficient mice had higher expression of transcripts encoding natriuretic peptides and nuclear factor (NF)-κB compared with wild-type mice. Again, IL-33 decreased expression of these genes in wild-type, but not ST2-deficient, mice. Given the role of the NF-κB system in the molecular pathogenesis of cardiac hypertrophy, these results suggest a potential mechanism for IL-33/ST2 signaling in mediating adverse remodeling and subsequent HF. Seki et al. [17] recently exposed rat myocytes to IL-33 in vitro, finding that IL-33 decreased caspase-3 activation (a critical step in the apoptotic cascade) and increased expression of the antiapoptotic gene *Bcl-2*. These antiapoptotic effects were attenuated by sST2 [17]. Therefore, the current understanding is that intact ST2 signaling plays a pivotal role in the ability of IL-33 to mediate cardiac pressure overload states.

## ST2 and Prognosis in Acute HF Syndromes

Clinically, measurement of sST2 has yielded great insights into the biological processes that lead to adverse outcomes across a wide spectrum of cardiac disease states. Indeed, a growing and significant body of literature has emerged in the past several years linking ST2 to deleterious correlates of cardiac structure and function in patients with acute HF syndromes with corresponding prognostic meaning.

Januzzi et al. [12] studied a group of 593 patients admitted to the emergency department with acute dyspnea with and without HF in the Pro-BNP Investigation of Dyspnea in the Emergency Department (PRIDE) study, with follow-up at 1 year for outcomes. Although sST2 concentrations did not predict a diagnosis of HF as well as NT-proBNP, concentrations of sST2 were nonetheless significantly higher in patients with acute HF compared with patients with non-HF dyspnea (0.50 vs 0.15 ng/mL; $P<0.001$), and the risk of a HF diagnosis was higher in patients in the highest deciles of sST2. Importantly, the prognostic meaning of sST2 was considerable: concentrations of the marker were higher in patients who were dead at 1 year compared with survivors (1.08 vs 0.18 ng/mL; $P<0.001$). There was a dose-dependent relationship between sST2 concentrations and risk of death at 1 year, and in multivariate regression analysis for predictors of death at 1 year, an sST2 concentration greater than 0.20 ng/mL strongly predicted 1-year mortality in patients with and without HF.

Notably, the prognostic value of sST2 was additive to that of NT-proBNP, such that patients with elevations in both NT-proBNP and sST2 experienced the highest rate of mortality at 1 year. Those with a low sST2 and high NT-proBNP or those with a high sST2 and low NT-proBNP had intermediate levels. Subjects with low values for both markers had the best short-term prognosis. Examining patients as a function of sST2 and NT-proBNP values, the risk of death (regardless of HF or non-HF cause of dyspnea) emerged almost immediately after enrollment and continued to increase with time. This association between sST2 and NT-proBNP with prognosis remains intact out to 4 years from presentation (Fig. 1).

In a study of 346 patients with acute HF from the PRIDE study and a similar cohort of patients from Linz, Austria [18], Rehman et al. [11] examined the association between sST2 concentrations and clinical characteristics and prognosis. sST2 concentrations at presentation correlated with New York Heart Association functional class, left ventricular ejection fraction ($r=0.13$), creatinine clearance ($r=0.22$), BNP ($r=0.29$), NT-proBNP ($r=0.41$), and C-reactive protein ($r=0.43$; all $P<0.05$). Unlike natriuretic peptides, sST2 levels were not related to age, prior diagnosis of HF, body mass index (BMI), atrial fibrillation, or etiology of cardiomyopathy (ischemic vs nonischemic).

As evidenced in the PRIDE study, sST2 levels were higher in patients with acute HF who died at 1 year. In multivariate Cox regression analysis of independent predictors of death, sST2 was associated with a twofold risk of mortality independent of other clinical and biochemical parameters of risk (including natriuretic peptide levels), and

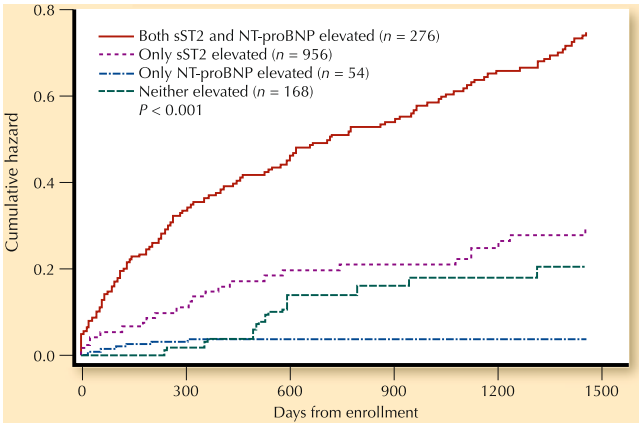


**Fig. 1** Association among elevated soluble ST2 (sST2) concentrations, N-terminal prohormone brain natriuretic peptide (NT-proBNP) values, and mortality following acute heart failure presentation. sST2 values show strong additive value to natriuretic peptides out to 4 years from presentation

the impact of sST2 concentration on admission on 1-year mortality was similar in patients with preserved and depressed left ventricular function. Patients with both an elevated sST2 and NT-proBNP level experienced the highest risk of death at 1 year (> 40%), whereas patients with both biomarkers below the median levels experienced a remarkably low mortality (< 10%). Interestingly, a high sST2 level reclassified risk of death in patients with a low natriuretic peptide level, suggesting that sST2 significantly augments traditional markers of risk stratification in acute HF. Moreover, in patients with an sST2 level lower than 0.49 ng/mL (the median level in the combined PRIDE and Linz cohort), a high natriuretic peptide level did not forecast 1-year mortality.

Regarding the composite operating characteristics for sST2 in the prediction of 1-year mortality, an sST2 level greater than 0.49 ng/mL had a 72% sensitivity, 56% specificity, a positive predictive value 39%, and negative predictive value 84%. Using the PRIDE cutoff median level greater than 0.20 ng/mL, a negative predictive value 96% for 1-year mortality emerged.

## ST2 and Cardiac Structure, Function, and Long-Term Mortality

A recent study by Shah et al. [19••] clarified a number of issues regarding sST2 in patients with acute HF, specifically examining the relationships between sST2 levels, cardiac structure, and function (as demonstrated by echocardiography), and longer-term mortality in patients with acute dyspnea. Of the initial PRIDE cohort, 139 patients had detailed two-dimensional echocardiography during index admission (median 45 hours after admission), with follow-up at 4 years for vital status. Patients were predominantly older (69 ± 14 y), overweight (BMI, 28.5± 6.5 kg/m$^2$), with preserved hemodynamics on admission (systolic blood pressure, 140 ± 28 mm Hg). A diagnosis of acute HF as the cause of dyspnea was adjudicated in 66%, with 34% having a prior history of HF.

sST2 concentrations were associated with higher LV end-systolic dimensions and volumes, poorer LV ejection fraction, less right ventricular (RV) fractional area change ($P$=−0.18; $P$=0.046), higher RV systolic pressure ($P$=0.26; $P$=0.005), and hypokinesis ($P$<0.001). In multivariate regression, independent predictors of ST2 included RV systolic pressure ($t$=2.29; $P$=0.002), LV ejection fraction ($t$=2.15; $P$=0.05) and dimensions (end-systolic, $t$=2.57; end-diastolic, $t$=2.98; both $P$<0.05), NT-proBNP ($t$=3.31; $P$= 0.009), heart rate ($t$=2.59; $P$=0.01), and presence of jugular venous distension ($t$=2.00; $P$=0.05; Table 1). These data link the basic science data suggesting a role for ST2 biology in the genesis of adverse ventricular remodeling with clinical stigmata of the process, including the deleterious association with prognosis: indeed, sST2 was higher in patients who were dead at 4 years versus survivors (0.48 vs 0.36 ng/mL; $P$=0.04), and in a Cox proportional hazards model that included echocardiographic results and other biomarkers, sST2 predicted death at 4 years independent of other traditional clinical, biochemical, and echocardiographic markers of risk (HR=2.70; $P$=0.003).

Despite unavoidable delays to echocardiography in this small population and potentially a referral bias (higher sST2 levels in patients referred for echocardiography versus those managed without echocardiography), these results suggest significant associations between sST2 and ventric-

**Table 1** Clinical and echocardiographic correlates of elevated soluble ST2 concentrations among patients with acute dyspnea

| Covariate | T | *P* value |
|---|---|---|
| NT-proBNP | 3.31 | 0.009 |
| RV systolic pressure | 2.29 | 0.002 |
| Transmitral E to tissue Doppler E/A ratio | −2.13 | 0.03 |
| Tissue Doppler A wave peak velocity | 2.11 | 0.05 |
| LV ejection fraction | 2.15 | 0.05 |
| LV end-diastolic dimension | 2.98 | 0.005 |
| LV end-systolic dimension | 2.57 | 0.01 |
| Heart rate | 2.59 | 0.01 |
| Jugular venous distension | 2.00 | 0.05 |

*Doppler E/A* early (E) to late atrial (A) mitral Doppler peak flow velocity, *LV* left ventricular, *NT-proBNP* N-terminal prohormone brain natriuretic peptide, *RV* right ventricular

(*From* Shah et al. [19••])

ular remodeling and long-term mortality independent of other markers of risk.

## ST2 and Monitoring in Acute and Chronic HF Syndromes

In the wake of evidence suggesting a potential role for serial natriuretic peptide concentrations in monitoring in acute and chronic HF [5, 20-24], emerging research has investigated a similar role for sST2 [25]. In 150 patients in a Veterans Administration Medical Center admitted for acute HF, levels of sST2 drawn serially during hospital stay were related to 90-day mortality. Interestingly, similar to results with NT-proBNP, patients who experienced a decrease in sST2 concentration greater than 15.5% during the index hospitalization experienced a low (7%) risk of death, whereas patients who did not have a decrease in sST2 concentration had a dramatically higher (33%) risk of death. The impact of sST2 changes during hospitalization on 90-day mortality was independent of natriuretic peptide levels. In addition, in patients with chronic advanced HF, increases in serially measured sST2 concentrations predict defibrillator therapies and sudden death (Januzzi, Personal communication).

Data from the PROTECT study (NCT00351390) investigating the impact of sST2 on outcomes in outpatient chronic HF management will clarify whether serial sST2 measurement in chronic HF will be clinically useful beyond standard, intensive HF management.

## ST2 and Implications on Pathophysiology of HF

Although recent evidence has securely established associations between sST2 concentrations, mortality, and cardiac structure, the source of circulating sST2 in patients with acute and chronic HF remains unclear. Relationships between biventricular function and HF diagnosis and sST2, along with in vitro evidence linking biomechanical stress to IL-33/ST2 and cardiac hypertrophy, a putative mechanism would involve poor ventricular function leading to increased wall stress as a stimulus for sST2 release. Alternatively, analogous to the in vitro proposal of negative feedback between soluble, circulating ST2 and IL-33 by Sanada et al. [16••], excessive circulating sST2 may actually be a decoy to bind circulating IL-33 and prevent its binding to ST2L, leading to unchecked fibrosis, hypertrophy, and transition to frank HF.

Bartunek et al. [26] recently studied sST2 in patients with aortic stenosis and LV hypertrophy and chronic HF, measuring the myocardial production of sST2 via a "myocardial gradient" between coronary sinus and arterial blood. Although myocardial ST2 mRNA production has been demonstrated in prior studies, there was no gradient of ST2 across the myocardium, suggesting the possibility that significant ST2 production occurs outside the heart. Importantly, these patients were not acutely destabilized, accordingly, the levels of sST2 measured in the study by Bartunek et al. [26] were in a range of great imprecision with older versions of the sST2 assay, which calls their result into question.

## ST2 and Acute Coronary Syndromes

In the current AHA HF Stages, patients with acute coronary syndromes are considered stage A (at risk), stage B (asymptomatic HF), or stage C/D (symptomatic HF). Furthermore, as acute coronary syndromes are perhaps one of the highest risk situations to rapidly traverse from stage A through C/D, identification of biological markers that identify those at highest risk for progressive HF is of utmost importance.

Shimpo et al. [9] investigated sST2 levels in 810 patients in the Thrombolysis In Myocardial Infarction (TIMI) 14 and Enoxaparin and TNK-tPA With or Without GPIIb/IIIa Inhibitor as Reperfusion Strategy in STEMI (ENTIRE)-TIMI 23 clinical trials, finding that sST2 concentrations were higher in patients who died or experienced new HF at 1 month. sST2 levels were associated with a more decompensated hemodynamic and inflammatory/ischemic profile on admission, with a positive association with heart rate, cardiac troponin I level, C-reactive protein, BNP, and serum creatinine. Higher levels of sST2 predicted death or a composite of death and new HF at 1 month independent of traditional clinical risk factors.

Sabatine et al. [8] extended these results in a study of 1239 patients with ST-segment elevation myocardial infarction in the Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis in Myocardial Infarction 28 (CLARITY-TIMI 28) trial. In this analysis, sST2 was again found to be independent of traditional clinical risk factors, including age, presence of hypertension, prior myocardial infarction, or HF. Patients with poorer TIMI flow or myocardial perfusion grade and patients who experienced cardiovascular death, new HF, or a composite of death or HF had higher levels of sST2. Values for sST2 were related to cardiovascular death or HF in a dose-dependent fashion, independent of NT-proBNP concentrations. Patients in the highest quartile of sST2 concentration had a nearly 3.5-fold risk of cardiovascular death or HF at 30 days compared with patients in the lowest quartile. Similar to studies in HF, the impact of elevated sST2 was additive to NT-proBNP levels, with patients in the highest quartiles of both sST2 and NT-proBNP levels experiencing the poorest 30-day

outcome (a 6.5-fold risk of death or HF). In a receiver-operator characteristic model involving both NT-proBNP and sST2 levels, discrimination for a composite cardiovascular death or HF was significantly improved, compared with clinical characteristics alone.

## Conclusions

Since its discovery as a gene product induced by cardiomyocyte stretch in vitro, ST2 has emerged as a powerful player with IL-33 in modulating ventricular function and remodeling via effects on apoptosis, inflammation, and myocardial fibrosis. Clinically, measurement of sST2 appears promising as a biomarker for remodeling and outcome across the AHA HF Stages. Circulating levels of sST2 are strongly related to short-and long-term post-discharge mortality in acute coronary syndromes and acute and chronic HF, as well as markers of cardiac structure and function. Ongoing research examining a role for serial assessment of sST2 concentrations in chronic HF will establish whether this biomarker has incremental utility beyond standard HF management. These efforts will be bolstered by the recent development of a novel, high-sensitivity sST2 assay that will allow for detection of sST2 concentrations in much lower concentrations [27••]. This will allow for study of sST2 in normal subjects, as well as in HF patients during states of stability with much more precision than prior iterations of the ST2 assay. In addition, new investigation into myocardial production of ST2 in acute HF states, as well as extension of ST2 into more advanced HF (eg, pre-transplantation evaluation, post-transplantation outcomes) will further establish the role of this novel biomarker of remodeling in HF. Ultimately, strategies targeting the deleterious phenotype predicted by sST2 values (eg, drug treatments that reduce the remodeling predicted by sST2 elevation) will follow.

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No further potential conflict of interest relevant to this article was reported.

## References

Papers of particular interest, published recently, have been highlighted as:

•• Of major importance

1. Daniels L, Maisel AS: Natriuretic peptides. J Am Coll Cardiol 2007, 50:2357–2368.
2. Liang F, Gardner DG: Mechanical strain activates BNP gene transcription through a p38/NF-κB-dependent mechanism. J Clin Invest 1999, 101:1603–1612.
3. Fonarow GC, Peacock WF, Phillips CO, et al.: Admission B-type natriuretic peptide levels and in-hospital mortality in acute decompensated heart failure. J Am Coll Cardiol 2007, 49:1943–1950.
4. Chen AA, Wood MJ, Krauser DG, et al.: NT-proBNP levels, echocardiographic findings, and outcomes in breathless patients: results from the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) echocardiographic substudy. Eur Heart J 2006, 27:839–845.
5. Bettencourt P, Ferreira S, Azevedo A, Ferreira A: Preliminary data on the potential usefulness of B-type natriuretic peptide levels in predicting outcome after hospital discharge in patients with heart failure. Am J Med 2002, 113:215–219.
6. Logeart D, Thabut G, Jourdain P, et al.: Predischarge B-type natriuretic peptide assay for identifying patients at high risk for re-admission after decompensated heart failure. J Am Coll Cardiol 2004, 43:635–641.
7. Weinberg EO, Shimpo M, De Keulenaer GW, et al.: Expression and regulation of ST2, an interleukin-1 receptor family member, in cardiomyocytes and myocardial infarction. Circulation 2002, 106:2961–2966.
8. Sabatine MS, Morrow DA, Higgins LJ, et al.: Complementary roles for biomarkers of biomechanical strain ST2 and N-terminal prohormone B-type natriuretic peptide in patients with ST-elevation myocardial infarction. Circulation 2008, 117:1936–1944.
9. Shimpo M, Morrow DA, Weinberg EO, et al.: Serum levels of the interleukin-1 receptor family member ST2 predict mortality and clinical outcome in acute myocardial infarction. Circulation 2004, 109:2186–2190.
10. Weinberg EO, Shimpo M, Hurwitz S, et al.: Identification of serum soluble ST2 receptor as a novel heart failure biomarker. Circulation 2003, 107:721–726.
11. Rehman SU, Mueller T, Januzzi JL Jr: Characteristics of the novel interleukin family biomarker ST2 in patients with acute heart failure. J Am Coll Cardiol 2008, 52:1458–1465.
12. Januzzi JL Jr, Peacock WF, Maisel AS, et al.: Measurement of the interleukin family member ST2 in patients with acute dyspnea: results from the PRIDE study. J Am Coll Cardiol 2007, 50:607–613.
13. Myeller T, et al.: Increased plasma concentrations of soluble ST2 are predictive for 1-year mortality in patients with acute destabilized heart failure. Clin Chem 2008, S4:752–756.
14. Iwahana H, Yanagisawa K, Ito-Kosaka A, et al.: Different promoter usage and multiple transcription initiation sites of the interleukin-1 receptor-related human ST2 gene in UT-7 and TM12 cells. Eur J Biochem 1999, 264:397–406.
15. Coyle AJ, Lloyd C, Tian J, et al.: Crucial role of the interleukin 1 receptor family member T1/ST2 in T helper cell type 2-mediated lung mucosal immune responses. J Exp Med 1999, 190:895–902.
16. •• Sanada S, Hakuno D, Higgins LJ, et al.: IL-33 and ST2 comprise a critical biomechanically induced and cardioprotective signaling system. J Clin Invest 2007, 117:1538–1549. *This report extensively details the relationship between ST2 and IL-33 in in vitro and in vivo model, providing a potential mechanism for elevated ST2 concentrations in adverse cardiac remodeling.*
17. Seki K, Sanada S, Kudinova AY, et al.: Interleukin-33 prevents apoptosis and improves survival after experimental myocardial infarction through ST2 signaling. Circ Heart Fail 2009, 2:684–691.
18. Mueller T, Dieplinger B, Gegenhuber A, et al.: Increased plasma concentrations of soluble ST2 are predictive for 1-year mortality in patients with acute destabilized heart failure. Clin Chem 2008, S4:752–756.
19. •• Shah RV, Chen-Tournoux AA, Picard MH, et al.: Serum levels of the interleukin- 1 receptor family member ST2, cardiac structure and function, and long-term mortality in patients with

acute dyspnea. Circulation: Heart Failure 2009, 2:311–319. *This is an echocardiographic analysis of the PRIDE study that details the significant relationships between sST2 level and markers of right ventricular and left ventricular systolic and diastolic function, as well as the long-term prognostic import of an elevated admission sST2 level*.

20. Bayés-Genís A, Santaló-Bel M, Zapico-Muñiz E, et al.: N-terminal pro-brain natriuretic peptide (NT-proBNP) in the emergency diagnosis and in-hospital monitoring of patients with dyspnoea and ventricular dysfunction. Eur J Heart Fail 2004, 6:301–308.
21. Jourdain P, Jondeau G, Funck F, et al.: Plasma brain natriuretic peptide-guided therapy to improve outcome in heart failure: the STARS-BNP Multicenter Study. J Am Coll Cardiol 2007, 49:1733–1739.
22. Pfisterer M, Buser P, Rickli H, et al.: BNP-guided vs symptom-guided heart failure therapy: the Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF) randomized trial. JAMA 2009, 301:383–392.
23. Shah M: STARBRITE: A randomized pilot trial of BNP-guided therapy in patients with advanced heart failure. Circulation 2006, 114:II528.
24. Troughton RW, Frampton CM, Yandle TG, et al.: Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. Lancet 2000, 355:1126–1130.
25. Boisot S, et al.: Serial sampling of ST2 predicts 90-day mortality following destabilized heart failure. J Card Fail 2008, 14:732–738.
26. Bartunek J, Delrue L, Van Durme F, et al.: Nonmyocardial production of ST2 protein in human hypertrophy and failure is related to diastolic load. J Am Coll Cardiol 2008, 52:2166–2174.
27. •• Dieplinger B, Januzzi JL Jr, Steinmair M, et al.: Analytical and clinical evaluation of a novel high-sensitivity assay for measurement of soluble ST2 in human plasma—The Presage ST2 assay. Clinica Chimica Acta 2009, 409:33–40. *This report details a novel, high-sensitivity assay used to measure ST2 concentrations*.