Original Article

Soluble Concentrations of the Interleukin Receptor Family Member ST2 and β-Blocker Therapy in Chronic Heart Failure

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Background**—**Concentrations of soluble (s)ST2 predict prognosis in heart failure. We recently found changing doses of β-blocker (BB) may affect sST2 concentrations. It remains unclear whether sST2 concentrations identify benefit of BB therapy, however.

Methods and Results**—**A total of 151 subjects with heart failure attributable to left ventricular systolic dysfunction were examined in this post hoc analysis; >96% were taking BB at enrollment. Medication regimen and sST2 values were obtained during 10 months. Cardiovascular events were examined as a function of baseline sST2 status (low ≤35 versus high >35 ng/mL) and final achieved BB dose (high ≥50 versus low <50 mg daily equivalent dose of metoprolol succinate). Patients with low sST2 titrated to high-dose BB had the lowest cardiovascular event rate at 0.53 events (P=0.001), and lowest cumulative hazard (P=0.003). Those with low sST2/low-dose BB, or high sST2/high-dose BB had intermediate outcomes (0.92 and 1.19 events). Patients with high sST2 treated with low-dose BB had the highest cardiovascular event rate (2.08 events) and the highest cumulative hazard. Compared with low sST2/high-dose BB, those with high sST2 treated with low-dose BB had an odds ratio of 6.77 (P<0.001) for a cardiovascular event. Patients with low sST2/low-dose BB or high sST2/high-dose BB had intermediate odds ratios for cardiovascular events (P=0.18 and 0.02). Similar results were found for heart failure hospitalization and cardiovascular death.

Conclusions**—**Although BB therapy exerted dose-related benefits across all study participants, sST2 measurement identifies patients with chronic heart failure who may particularly benefit from higher BB doses.

Clinical Trial Registration**—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT00351390.

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Key Words: β-adrenergic blockers ■ biological markers ■ heart failure ■ prognosis

Myocardial insult, remodeling and neurohormonal activation are intricately involved in the development and progression of heart failure (HF). A growing number of biomarkers, found at every step of these pathways, can provide important biological information regarding these deleterious processes and may aid in the prediction of onset, diagnosis, risk stratification and potentially monitoring therapy in HF. One such biomarker is the interleukin receptor family member, ST2.

Clinical Perspective on p 1213

Genomic studies noted that the ST2 gene is strongly induced by mechanical strain on cardiac fibroblasts and cardiomyocytes.[1] The product of this gene leads to a membrane-bound receptor (ST2L) as well as a soluble form of ST2 (sST2). Concentrations of sST2 are increased in circulation in conditions of cardiac stress such as acute and chronic HF and were found to be closely associated with adverse left ventricular (LV) remodeling and poor prognosis.[2,3] However, the exact mechanism of sST2 in HF remodeling and decompensation remains unclear.

Interestingly, a change in sST2 over time with aggressive HF therapy seems to be strongly prognostic of future outcomes[4] and therapies that mitigate LV remodeling may potentially benefit patients with elevated sST2.[5] To date, a number of chronic HF medications have been shown to improve LV remodeling including β-adrenergic blockers (BB), angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists.[6–9] Short of a single report,[5] however, little is known about the potential interplay between antiremodeling therapies and sST2 values in high-risk patients.

Among a population of study participants with LV systolic dysfunction (LVSD), we recently showed that change in sST2 concentration was associated with LV remodeling as well as risk for cardiovascular events. Notably, of

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all therapies examined, we demonstrated that change in BB dose among these study participants was directly associated with a change in subsequent sST2; the biomarker was also associated with change in ventricular remodeling indices.[10] However, in-depth understanding of the prognostic interaction between BB and sST2 values is lacking. It is in this context that we aimed to better characterize this interplay between sST2 and BB therapy in the cohort from the ProBNP Outpatient Tailored Chronic Heart Failure (PROTECT) study.[11]

Methods

Study Design and Patient Population

A prospective, randomized, controlled, single-center trial, the PROTECT study examined 151 patients with LVSD (LV ejection fraction, ≤40%), New York Heart Association (NYHA) functional class II to IV and a recent HF decompensation (<6 months) to evaluate the efficacy of N-terminal pro-B-type natriuretic peptide (NT-proBNP)–guided HF management versus standard HF care >10 months.[11] The primary end point assessed was total cardiovascular events, a composite outcome defined as worsening HF (new or worsening symptoms/signs of HF requiring unplanned intensification of decongestive therapy), hospitalization for acutely decompensated HF, clinically significant ventricular arrhythmia, acute coronary syndrome, cerebral ischemia, and cardiac death. All patients gave informed consent, and the Partners Healthcare Institutional Review Board approved all study procedures.

Study Procedures

A detailed medication list and a blood sample for routine laboratory tests and sST2 measurements were obtained at each clinic visit from baseline through the follow-up period. Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation.[12] As previously described,[13] medications were adjusted at each clinic visit to achieve guideline-derived HF therapy.

Biomarker Measurement

Plasma was sampled at each visit and stored at −80°C with a single freeze–thaw cycle. sST2 was measured using the highly sensitive Presage ST2 Assay (Critical Diagnostics, San Diego, CA; coefficient of variation, ≤1.4%), and NT-proBNP was measured using Elecsys proBNP assays (Roche Diagnostics, Indianapolis, IN); 145 patients had ≥2 plasma samples.

Prognostic Thresholds for sST2

A previously identified prognostic threshold of 35 ng/mL was used as the threshold of risk for sST2 in the present analysis[3]; patient response was defined as achievement of a concentration ≤35 ng/mL, whereas nonresponse was defined as sST2>35 ng/mL. We defined percentage time in response for sST2 as the proportion of time with sST2≤35 ng/mL relative to the total time enrolled in the study.

β-Blockers

All BB doses were converted to total daily dose of metoprolol succinate extended release equivalents from each BB total daily dose.[11] One milligram total daily dose of metoprolol succinate extended release was considered equivalent to the following total daily dose: metoprolol tartrate immediate release, atenolol *2, carvedilol *4, bisoprolol *20, propranolol *0.833, nadolol *0.833, labetalol/4, sotalol/1.2.

As noted, significant uptitration of BB dosing was performed in the PROTECT study, with achieved doses entirely comparable with other contemporary trials in HF attributable to LVSD.[14] Overall, median achieved BB dose for the cohort was 50 mg of metoprolol succinate extended release equivalent; this dose was used as a cutoff value to define high-dose BB therapy versus low-dose BB therapy because the next dose above is consistent with 50% of goal doses from clinical practice guidelines.[15]

Statistics

Categorical variables between 2 groups were compared using the χ^2 test, and continuous variables were compared using Student *t*, Mann–Whitney *U*, or Kruskal–Wallis test, as appropriate. Normally distributed continuous variables were summarized using means±SD, whereas in the context of non-normality, medians (25th, 75th percentile) were used. Repeated measures were analyzed using Wilcoxon tests.

The patient cohort was divided into 4 groups according to the baseline sST2 values (≤35 or >35 ng/mL) and final achieved BB dose (≥50 versus <50 mg/d), and the difference in cardiovascular events between these 4 groups was determined using Kruskal–Wallis test.

Univariable and multivariable logistic regression analyses were performed, modeling the association between baseline sST2 values, final achieved BB dose, and the presence of any cardiovascular events. The interaction between sST2 and final achieved BB dose was assessed. The multivariable model was initially created with both baseline sST2 status and final achieved BB dose status forced in, then forward stepwise selection was used to choose the optimal predictors of cardiovascular events. Variables considered for inclusion in the multivariable models were age, sex, ischemic cardiomyopathy, atrial fibrillation or flutter, NYHA class III or IV, baseline heart rate (HR), baseline NT-proBNP, and baseline eGFR. Odds ratios were determined from logistic regression models.

Next, time-to-first cardiovascular event estimates were calculated using cumulative hazard methodology. Patients who did not experience any cardiovascular events were censored at the earlier of 1 year or the date last known to be event-free. Comparisons were made using the log-rank test.

In all statistical analyses, a 2-tailed *P* value <0.05 was considered to indicate statistical significance. All analyses were performed with SAS (version 9.2; Cary, NC) or PASW (versions 17 and 18; Chicago, IL) software.

Results

There was a total of 160 end points in the PROTECT study with 59 patients having ≥1 event. Total number of events for the PROTECT study[11] was updated to reflect a correction to a coding issue.

Baseline Characteristics

The study cohort was divided into 4 groups according to each patient's baseline sST2 values (≤35 versus >35 ng/mL) and final achieved BB dose (≥50 versus <50 mg/d) (Table 1). Although there were no statistically significant differences in the 4 groups in study arm allocation, there were potential differences in age and sex (both *P*=0.06). Patients with low baseline sST2 values who had low final BB dose tended to be older than the rest of the group, and there were higher percentage of male in the group of patients with high sST2 values at baseline. There were slightly more non-whites in the group with low baseline sST2 who subsequently achieved higher BB doses (*P*=0.04). There were no overall significant differences in LV ejection fraction, NYHA class and medical history of ischemic cardiomyopathy, atrial fibrillation, hypertension, or diabetes mellitus. However, patients who were titrated to low BB doses tended to have more severe HF, as evidenced by higher proportion of patients with NYHA class III and IV.

Table 1. Baseline Characteristics by sST2 and Final Achieved BB Dose

Variable	Low sST2 (≤35), High BB (≥50) (n=58)	Low sST2 (≤35), Low BB (<50) (n=12)	High sST2 (>35), High BB (≥50) (n=57)	High sST2 (>35), Low BB (<50) (n=24)	*P* Value
Age, y	62.1 (12.9)	73.6 (9.5)	62.0 (15.3)	64.3 (13.3)	0.06
Sex (men)	43 (75.4%)	9 (75.0%)	53 (91.4%)	22 (91.7%)	0.06
Race (white)	44 (77.2%)	12 (100.0%)	54 (93.1%)	21 (87.5%)	0.04
Study arm (NT-proBNP guided)	28 (49.1%)	4 (33.3%)	29 (50.0%)	14 (58.3%)	0.57
LVEF	28.1 (8.8)	29.8 (7.9)	27.6 (9.3)	23.7 (8.4)	0.28
NYHA					
Class II	29 (50.9%)	2 (16.7%)	29 (50.0%)	8 (33.3%)	0.17
Class III	22 (38.6%)	9 (75.0%)	20 (34.5%)	12 (50.0%)	
Class IV	6 (10.5%)	1 (8.3%)	9 (15.5%)	4 (16.7%)	
Medical history					
ICMP	25 (43.9%)	8 (66.7%)	28 (48.3%)	15 (62.5%)	0.29
AF	19 (33.3%)	6 (50.0%)	22 (37.9%)	14 (58.3%)	0.17
HTN	30 (52.6%)	4 (33.3%)	34 (58.6%)	11 (45.8%)	0.38
Diabetes mellitus	20 (35.1%)	7 (58.3%)	25 (43.1%)	11 (45.8%)	0.46
Examination					
BMI	29.6 (6.2)	29.0 (7.1)	28.6 (6.1)	26.1 (5.6)	0.13
Heart rate	72.6 (12.6)	73.9 (12.2)	72.9 (12.7)	75.8 (11.8)	0.73
Systolic BP	111.1 (14.5)	109.9 (13.3)	110.6 (15.9)	102.0 (12.2)	0.07
JVD	15 (26.3%)	5 (41.7%)	21 (36.2%)	13 (54.2%)	0.12
Rales	5 (8.8%)	4 (33.3%)	6 (10.3%)	4 (16.7%)	0.11
Edema	10 (17.5%)	6 (50.0%)	20 (34.5%)	11 (45.8%)	0.02
Laboratory results					
eGFR	63.6 (19.3)	51.0 (13.9)	62.6 (24.0)	54.0 (16.5)	0.08
NT-proBNP	2024 (557.0, 2570.5)	3619 (1692.5, 2773.5)	3330 (1208.0, 4318.0)	6606 (1762.0, 7739.0)	0.03
Baseline meds					
ACE	42 (73.7%)	9 (75.0%)	39 (67.2%)	10 (41.7%)	0.04
ARB	8 (14.0%)	1 (8.3%)	10 (17.2%)	4 (16.7%)	0.87
MRA	24 (42.1%)	3 (25.0%)	21 (36.2%)	15 (62.5%)	0.1
β-Blocker	57 (100.0%)	7 (58.3%)	58 (100.0%)	23 (95.8%)	<0.001
Diuretics	52 (91.2%)	11 (91.7%)	52 (89.7%)	23 (95.8%)	0.84
Follow-up, d	340 (199, 377)	361 (351, 389)	355 (187, 392)	359 (181, 374)	0.77

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blockers; AF, atrial fibrillation; BB, β-blocker; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HTN, hypertension; ICMP, ischemic cardiomyopathy; JVD, jugular venous distension; LVEG, left ventricular ejection fraction, MRA, mineralocorticoid receptor antagonists; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; and sST2, soluble form of ST2.

Across study visits, patients with an elevated sST2 tended to have slightly lower systolic and diastolic blood pressure levels but similar HR when compared with those with lower sST2. Overall, there were no significant differences in physical examination findings with the exception of edema; the group with low baseline sST2 who achieved high BB dose were least likely to have edema (*P*=0.02). Although there were no overall differences between the groups in renal function, patients who were titrated to low BB dose tended to have slightly lower eGFR.

There was a significant difference in baseline NT-proBNP values (*P*=0.03). Patients with low baseline sST2 values who were titrated to high BB dose had the lowest baseline NT-proBNP concentration (2024 [557, 2571] pg/mL), whereas patients with high baseline sST2 values who were not titrated to high-dose BB had the highest baseline NT-proBNP values (6606 [1762, 7739] pg/mL). The other 2 groups had intermediate values.

At baseline, the vast majority of study subjects were on a guideline-derived medication program; 81% were on angiotensin-converting enzyme inhibitors or angiotensin receptor blocker and 96% of the patients were on BB. There were no differences in the percentage of patients taking mineralocorticoid receptor antagonists or loop diuretics at baseline. Those with high baseline sST2 values not titrated to high-dose BB were less likely to take angiotensin-converting enzyme inhibitors at baseline (*P*=0.04). There were no significant differences in follow-up duration between 4 groups (*P*=0.77).

Table 2. Vital Signs at Quarterly Visits as a Function of Achieved β-Blocker Dose

	SBP			DBP			HR		
	Low-Dose BB	High-Dose BB	*P* Value	Low-Dose BB	High-Dose BB	*P* Value	Low-Dose BB	High-Dose BB	*P* Value
Baseline	102 [95–116]	110 [100–120]	0.04	60 [60–62]	68 [60–72]	<0.001	74 [69–82]	70 [64–80]	0.22
3 mo	107 [94–120]	110 [100–122]	0.21	60 [58–70]	64 [60–72]	0.02	70 [61–83]	69 [60–76]	0.21
6 mo	104 [97–117]	110 [100–120]	0.16	60 [51–70]	64 [60–70]	0.03	70 [62–79]	68 [60–77]	0.54
9 mo	106 [90–114]	112 [104–124]	0.01	60 [52–67]	64 [60–74]	0.01	68 [60–74]	66 [60–76]	0.89
12 mo	111 [100–123]	111 [100–122]	0.66	60 [55–70]	64 [60–70]	0.03	73 [62–81]	66 [60–80]	0.09

BB indicates β-blocker; DBP, diastolic blood pressure; HR, heart rate; and SBP, systolic blood pressure.

Baseline sST2 Values and Final Achieved BB Dose

The median achieved dose of BB was similar for patients whose baseline sST2 was ≤35 versus >35 ng/mL (75 versus 50 mg metoprolol succinate extended release equivalent total daily dose; *P*=0.22).

Blood Pressure, HR, and Final BB Dose

As noted in Table 2, at each quarterly study visit, a small but occasionally statistically significant difference in systolic and diastolic blood pressure was present in those study participants who were not titrated to higher dose BB. Notably, HR was similar between groups at each visit.

Cardiovascular Events by Baseline sST2 and Final BB Dose

There were significant differences between groups as stratified by baseline sST2 values and final achieved BB dose (Figure 1; *P*=0.001). The mean cardiovascular event rate was the lowest for patients with low baseline sST2 values who were titrated during the study to highest BB dose (0.53 events) and intermediate for patients with low sST2 values who were not titrated to high BB dose (0.92 events) and patients with elevated sST2 values titrated to high BB dose (1.19 events); the highest rate of events was seen in study participants with high sST2 concentrations at baseline who were not titrated to high BB dose (2.08 events).

Among patients titrated to high-dose BB, if baseline sST2 values were elevated, a markedly higher risk for cardiovascular events was seen compared with patients with low baseline sST2 values (odds ratio [OR], 2.5 versus referent). In a similar fashion, among study participants who were not titrated to high-dose BB by the end of the study, elevated baseline sST2 concentrations identified a group of patients at particularly higher risk compared with those with low baseline sST2 concentrations (OR, 6.0 versus 1.7). There was no interaction between sST2 and final achieved BB dose status (*P*=0.92).

Taken another way (Figure 2), patients with low baseline sST2 values and high-risk factors (such as low final BB dose or high baseline NT-proBNP values) had cardiovascular event rates similar to the overall group. Patients with high baseline sST2 values and other high-risk factors had higher cardiovascular event rates compared with patients with low baseline sST2 values and the same high-risk factors.

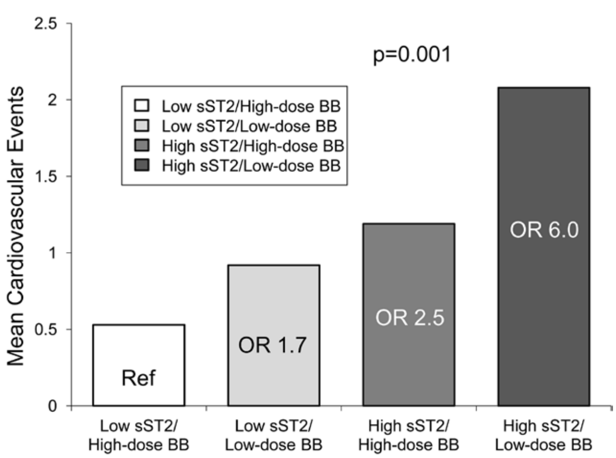

Figure 1. Mean cardiovascular events by baseline soluble form of ST2 (sST2) and final achieved β-blocker (BB) dose. OR indicates odds ratio.

Cumulative Hazard by Baseline sST2 and Achieved BB Dose

In cumulative hazard analyses (*P*=0.003; Figure 3), patients with low baseline sST2 values titrated to high-dose BB had the lowest consequent risk of cardiovascular events with time. Patents with low baseline sST2 values not titrated to high-dose BB had similar outcomes as those with high baseline sST2 values titrated to high-dose BB; both groups were at intermediate risk. At the highest risk with time were patients with highest baseline sST2 concentrations who were not subsequently titrated to high-dose BB therapy. Adding age and sex as covariates did not change the significance of the result of the cumulative hazard analyses (*P*=0.008).

Predictors of Cardiovascular Events

When baseline NT-proBNP or eGFR values were forced into a base model containing baseline sST2 status and achieved BB dose status, both baseline sST2 status and achieved BB dose status remained independently predictive of cardiovascular events. However, neither NT-proBNP nor eGFR were independent predictors of cardiovascular events in these models already containing baseline sST2 status and achieved BB dose status. When NYHA class III or IV status was added to the base model, NYHA class status was independently predictive of cardiovascular events (Table 3).

When all clinical and laboratory characteristics were included into a model predictive of cardiovascular events, significant predictors of outcomes were baseline sST2 value

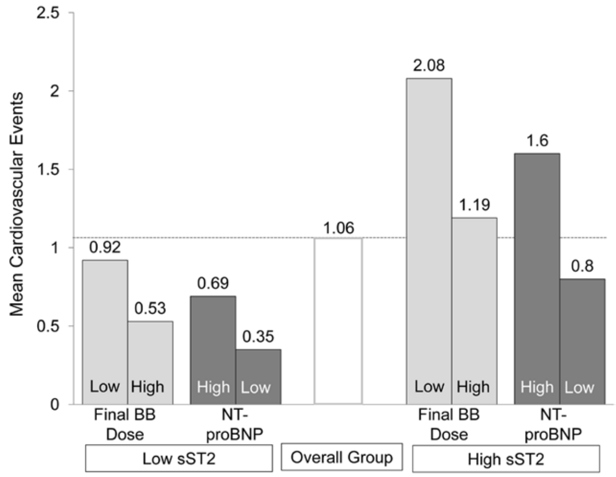

Figure 2. Cardiovascular events by low and high baseline soluble form of ST2 (sST2) values. Modification by β-blocker (BB) final dose and baseline N-terminal pro-B-type natriuretic peptide (NT-proBNP) value.

status (OR, 2.94 [95% confidence interval, 1.42, 6.10]), achieved BB dose status (high or low; OR, 2.26 [95% confidence interval, 1.01, 5.08]), and NYHA class 3 or 4 (OR, 2.20 [95% confidence interval, 1.06, 4.56]).

Discussion

We have previously reported the relationship between BB dose change and dynamic change in sST2 concentrations in patients with chronic HF attributable to LVSD.[10] In this post hoc analysis of the PROTECT study, the relationship between sST2 values and BB dosing was further examined by comparing cardiovascular event rates between patients with varying degree of risk as identified by baseline sST2 values with subsequent BB dose achieved with time. Although BB therapy exerted benefit across all strata of risk in the study, within categories of low or high-dose BB therapy, we found that we were able to identify patients who were particularly at high risk for cardiovascular events if their baseline sST2 values were >35 ng/mL. As a matter of fact, those with the highest risk for subsequent cardiovascular events were identified by an elevated baseline sST2 value, but this risk was not entirely realized in those titrated to higher dose BB. Within the context of a nonrandomized comparison, our proof-of-concept analysis suggests that biomarker concentrations may identify a risk that may theoretically be mitigated by specific drug therapy, raising the possibility that higher dose BB therapy may be particularly efficacious in the face of an elevated sST2. Another hypothesis-generating inference from these data may be that a low sST2 value may be protective against cardiovascular events in patients with other poor prognostic markers such as low achieved BB dose or high baseline NT-proBNP values.

It is worth noting that our data do not in any way suggest that BB therapy should be withheld when sST2 is low. Indeed, in patients with low sST2 values, cardiovascular event rates were further lowered when aggressive BB doses were achieved, and across baseline sST2 concentrations, the relative risk reduction was similar for when high-dose BB therapy was reached; nearly all subjects were receiving these guideline-derived medical therapy agents even at study entry. However, given the highest baseline risk of patients with elevated baseline sST2 concentrations, the absolute risk reduction seemed to be greater when higher doses of BB were subsequently achieved. Given the challenge of selecting therapies to titrate in HF and the difficulties achieving goal doses during such titration (indeed reflected in not only our data, but also contemporary analyses of modern HF care),[16] our data suggest potential value in considering sST2 levels to prompt an aggressive titration of BB in particular. This is not without significance; despite proven benefit of BB and vigorous support in clinical practice guidelines, the actual dose of BB achieved in standard practice is considerably lower than the guideline-recommended dose and comparable with the cutoff dose we defined for our analysis: a daily metoprolol succinate

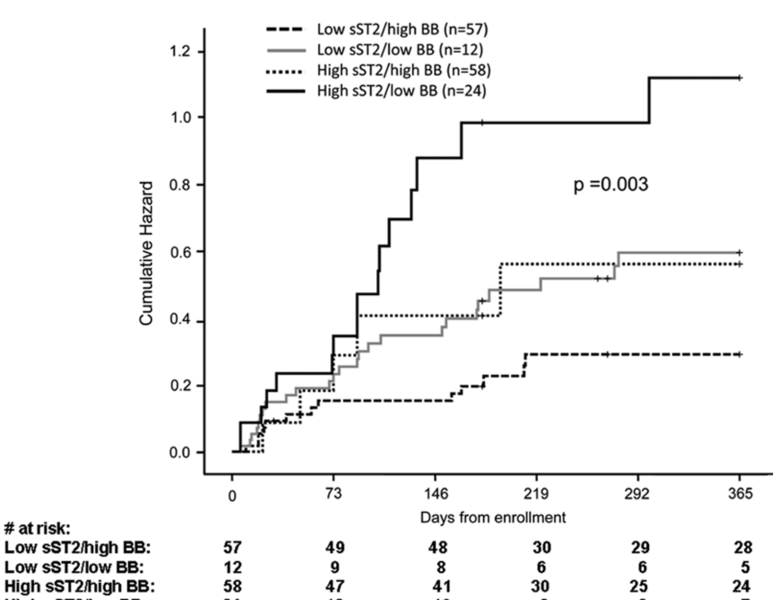

Figure 3. Cumulative hazard by baseline soluble form of ST2 (sST2) and final achieved β-blocker (BB) dose.

Table 3. Predictors of Cardiovascular Events

Variables in the Model	OR for CV event (95% CI)	*P* Values	Cox and Snell, Nagelkerke R^2	Model *P* Value
High baseline sST2 status	2.63 (1.30–5.26)	0.007	9.3%–12.6%	0.001
Low final BB status	2.56 (1.16–5.63)	0.02		
High baseline sST2 status	2.76 (1.38–5.52)	0.004	0.07%–0.09%	0.006
Final BB dose (continuous)	1.00 (0.99–1.00)	0.34		
High baseline sST2 status	2.51 (1.21–5.26)	0.01	10.8%–14.6%	0.001
Low final BB status	2.37 (1.05–5.33)	0.04		
Baseline log NT-proBNP	1.22 (0.86–1.72)	0.26		
High baseline sST2 status	2.65 (1.30–5.38)	0.007	11.0%–15.0%	0.001
Low final BB status	2.23 (1.00–4.99)	0.05		
eGFR	0.98 (0.97–1.00)	1.00		
High baseline sST2 status	2.79 (1.36–5.75)	0.005	12.3%–16.7%	<0.001
Low final BB status	2.19 (0.98–4.99)	0.06		
NYHA Class III or IV	2.28 (1.11–4.72)	0.03		

BB indicates β-blocker; CV, cardiovascular; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OR, odds ratio, and sST2, soluble form of ST2.

dose of 50 mg and carvedilol dose of 25 mg (both ≥50% lower than guideline recommendations).[16]

We found that systolic and diastolic blood pressure were slightly lower in those who were not titrated to higher dose BB, which may (in part) explain why such titration did not occur. However, although statistically significant, the clinical significance of this small difference in blood pressure is uncertain. Curiously, no significant difference in HR between the groups was noted. Although some patients with high baseline sST2 values or those who were not able to achieve high-dose BB had higher NT-proBNP, an established prognostic marker or lower eGFR, in multivariable regression model analyses, the differences in NT-proBNP or eGFR were not significant in the prediction of cardiovascular events. On the other hand, baseline NYHA classification status was significant in predicting cardiovascular events and the best model included NYHA class.

The putative link between sST2 and benefit of BB therapy requires clarification. Cardiac remodeling is a central feature in the development and progression of HF, a process that includes hypertrophy and apoptosis of cardiomyocytes, reinduction of fetal gene expression and alternations in the extracellular matrix including fibroblasts.[17] One of the critical factors in cardiac remodeling is the sympathetic nervous system; norepinephrine, the primary sympathetic neurotransmitter, acting through α- and β-adrenergic receptors, is thought to play a central role in initiating and sustaining cardiac remodeling. Increased norepinephrine concentrations and subsequent downregulation and desensitization of the cardiac β-adrenergic receptors stimulates the growth of cardiomyocytes,[18] causes the death of cardiac myocytes,[19] and stimulates fibroblast DNA and protein synthesis.[20] These are all processes that contribute to the progression of HF through remodeling, providing a biomechanical explanation for the use of medications that inhibit these pathways. The clinical and mechanical benefit of BB in chronic HF is well documented.[6,21,22] Acting directly through the β-adrenergic receptors, BB block the activation of the sympathetic nervous system and deter progression of HF through inhibiting adverse remodeling.[23] sST2 is produced by cardiac fibroblasts and by cardiomyocytes in conditions of increased cardiac injury and tension[1] and is intimately involved in cardiac remodeling as shown in experimental as well as clinical models.[10] The role of sST2 in remodeling seems to be mediated by its effect on its primary ligand, interleukin-33, which itself is also synthesized when cardiac fibroblasts are mechanically stretched. Interleukin-33 has been shown to inhibit cardiomyocyte hypertrophy, fibrosis, and apoptosis.[24,25] How BB may influence this complex physiology remains unclear but in need of further study.

Previous data from Weir et al[5] suggested that sST2 measurement may identify patients after myocardial infarction most likely to show beneficial LV remodeling with mineralocorticoid receptor antagonists therapy. In our cohort of study subjects with chronic LVSD, a slightly different population, we did not find an inter-relationship between mineralocorticoid receptor antagonists therapy and sST2 values. More information about sST2 at the molecular and cellular level is needed to definitively answer whether a link between sST2 and drug therapy is specific to either class of agents. Regardless, both our analysis and that of Weir et al[5] are proof-of-concept studies that show that sST2 may potentially be used to leverage specific therapies with benefit in the management of HF. Prospective randomized studies would be needed to confirm these associations.

Limitations of our analysis include the fact that this was a post hoc analysis and nonrandomized; given the lack of literature on this subject, findings from this study may inform the design of a prospective study further exploring the relationship between sST2 and BB therapy. The PROTECT study was a small study; however, the single-center nature of the analysis enabled our ability to characterize the patient cohort in detail with in-depth medication and event analysis, something lacking in many larger studies. Although nearly every subject was taking BB in the PROTECT study, a wide range of doses was observed, and one could argue that if every subject was titrated to goal doses of BB, our analysis would be meaningless. Our results would argue otherwise; sST2 identified risk even in those titrated to highest dose BB. Given the rising tide of polypharmacy in chronic HF and the manifest gaps in quality of care relative to agents such as BB,[16] we think our results inform potential value in guiding specific application of these agents. Finally, no study subjects in PROTECT were taking ivabradine, an agent specifically used to reduce HRs currently in use outside of the United States; given the interplay between ivabradine and BB in terms of clinician choice and effect on achieved doses of either agent, our data may be of significance.

In conclusion, extending the observation that sST2 values are affected by BB dosing, we now show that sST2 values also particularly identify different strata of risk based on subsequent achievement of BB dosing. As researchers in the field of chronic HF are now tentatively exploring the potential for biomarker-guided HF management, our data now open the possibility of prospectively exploring the use of sST2-guided BB therapy in chronic HF patients with LVSD.

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Disclosures

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CLINICAL PERSPECTIVE

Besides the natriuretic peptides, most established or emerging biomarkers of heart failure (HF) do not have clearly established links between changes in their concentrations relative to commonly used HF therapies. We recently reported that concentrations of the interleukin receptor family member soluble (s)ST2 were strongly prognostic in patients with chronic HF attributable to left ventricular systolic dysfunction and that adjustment in β-adrenergic blockers uniquely affected sST2 concentrations. Accordingly, in the present analysis, we sought to examine the interplay between sST2 concentrations and response to β blocker therapy. During a mean of 10 months of follow-up, we found uptitration to higher doses of β-adrenergic blockers was associated with better outcomes in all subjects, but the benefit of high-dose β-blocker was particularly evident in those with sST2 concentrations ≥35 pg/mL at enrollment. Those with a high sST2 at baseline treated with low-dose β-blocker had the highest event rates (mean of 2.08 events, including worsening HF, hospitalization or cardiovascular death), compared with 1.19 events in those with an elevated sST2 treated with higher dose β-blocker therapy. Compared with a referent group with low sST2 concentrations treated with high-dose β-blocker doses, the risk for cardiovascular events was 6.0 for those with high sST2/low dose β-blocker, and 2.5 for those with high sST2/high-dose β-blocker. In contrast, reduction in risk was more modest in those with low sST2 treated with higher dose β-blocker (odds ratio, 1.7; P=0.18). Thus, although β-blockers exerted dose-related benefits across all patients with left ventricular systolic dysfunction, reductions in cardiovascular events were most pronounced in those with elevated sST2 values. Elevated concentrations of sST2 may therefore identify patients with chronic HF who derive particularly significant benefits from higher dose β-blocker therapy.

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