Soluble ST2 for Prediction of Heart Failure and Cardiovascular Death in an Elderly, Community-Dwelling Population

Ravi H. Parikh, MD; Stephen L. Seliger, MD, MS; Robert Christenson, PhD; John S. Gottdiener, MD; Bruce M. Psaty, MD, PhD; Christopher R. deFilippi, MD

Background—Soluble ST2 (sST2), a marker of myocyte stretch and fibrosis, has prognostic value in many cardiovascular diseases. We hypothesized that sST2 levels are associated with incident heart failure (HF), including subtypes of preserved (HFP EF) and reduced (HFrEF) ejection fraction, and cardiovascular death.

Methods and Results—Baseline serum sST2 was measured in 3915 older, community-dwelling subjects from the Cardiovascular Health Study without prevalent HF. sST2 levels were associated with older age, male sex, black race, traditional cardiovascular risk factors, other biomarkers of inflammation, cardiac stretch, myocardial injury, and fibrosis, and abnormal echocardiographic parameters. In longitudinal analysis, greater sST2 was associated with a higher risk of incident HF and cardiovascular death; however, in multivariate models adjusting for other cardiac risk factors and the cardiac-specific biomarker, N-terminal pro–type B natriuretic peptide, these associations were attenuated. In these models, an sST2 level above the US Food and Drug Administration–approved cutoff value (>35 ng/mL) was significantly associated with incident HF (hazard ratio [HR], 1.20; 95% CI, 1.02–1.43) and cardiovascular death (HR, 1.21; 95% CI, 1.02–1.44), and greater sST2 was continuously associated with cardiovascular death (per 1-ln increment: HR, 1.24; 95% CI, 1.02–1.50). sST2 was not associated with the HF subtypes of HFpEF and HFrEF in adjusted analysis. Addition of sST2 to existing risk models of HF and cardiovascular death modestly improved discrimination and reclassification into a higher risk.

Conclusions—The predictive value of sST2 for HF of all subtypes and cardiovascular death is modest in an elderly population despite strong cross-sectional associations with risk factors and underlying cardiac pathology. (J Am Heart Assoc. 2016;5: e003188 doi: 10.1161/JAHA.115.003188)

Key Words: biomarker • epidemiology • heart failure • prediction statistics • survival

Given the significant economic, physical burden, and poor prognosis of heart failure (HF) in the United States, especially in older adults, it is important to identify factors that can predict risk of new-onset HF in a still asymptomatic population. The circulating biomarker, soluble ST2 (sST2) has been shown to be a powerful independent prognosticator for patients with acute myocardial infarction (AMI)1,2 as well as acute decompensated3,4 and chronic5–9 HF. sST2, a member of the interleukin (IL)-1 receptor-like family of proteins, is released in response to myocyte stretch, and functions as a decoy receptor, neutralizing its ligand, IL-33. A central role of IL-33 has been identified in cardiomyocytes protecting against progressive fibrosis and hypertrophy.10 Studies in patients with shortness of breath,11–14 chest pain,15 and those referred for outpatient echocardiograms16 have shown poorer prognosis among those with higher concentrations of circulating sST2, irrespective of the final clinical diagnosis. Among population-based studies, the Dallas Heart Study reported increased all-cause and cardiovascular mortality in younger and middle-aged adults with greater circulating sST2,17 and there was an increased risk of HF, death, and major cardiovascular events among middle-aged adults with greater sST2 in the Framingham Heart Study (FHS).18

Older adults (>65 years of age) represent a segment of the general population at greatest risk for incident HF, with rates approaching 10 per 1000 annually.19 Therefore, sST2 may be a particularly useful biomarker in this population for
cardiovascular risk stratification. Past work from our group and others has shown that sST2 is a powerful prognostic factor in patients with HF with preserved ejection fraction (HFrEF). This may be particularly relevant to older adults, where HFrEF comprises at least 50% of HF and is associated with a high burden of comorbidities, which may be associated with increased sST2 levels. We hypothesized that in a community-based elderly population free of HF, increased sST2 levels will be associated with increased incident HF and increased cardiovascular mortality. Furthermore, sST2 level, a nonspecific marker that also has been associated with noncardiac comorbidities, may be an adjunct to cardiac specific biomarkers to differentiate subjects at greater risk for HFrEF than HF with reduced ejection fraction (HFrEF).

Methods

Study Organization and Participants

We performed a longitudinal observational study utilizing stored serum samples from the multicenter Cardiovascular Health Study (CHS). Details of the design and methods of the CHS have been published previously. Briefly, study participants included community-dwelling adults ≥65 years enrolled at 4 participating centers. Participants (N=5201) initially enrolled in 1989–1990, and an black supplemental cohort (N=687) enrolled in 1992–1993. This ancillary analysis included participants without a previous diagnosis of HF in whom measures of amino terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin T (hs-cTnT) had already been performed as previously described and with available stored serum for measurement of sST2. Figure 1 is a flow diagram of CHS participants who met criteria or were excluded for the present sST2 analysis. The CHS was approved by the institutional review boards of the University of Washington (Seattle, WA) and participating centers. The present analysis was approved by the University of Maryland Baltimore Institutional Review Board (Baltimore, MD). All participants gave written informed consent.

Biomarker Analysis

sST2 was measured from previously frozen serum (−70°C) collected from participants in the main CHS cohort (either in 1992–1993 or 1995–1996) and the supplemental CHS black cohort (either in 1995–1996 or 1998–1999) using the US Food and Drug Administration (FDA)-approved Presage ST2 assay (Critical Diagnostics, San Diego, CA). The FDA-approved prognostic cutpoint for this assay is 35 ng/mL. References ranges for sST2 have been reported as 8.6 to 49.3 ng/mL in males and 7.2 to 33.5 ng/mL in females or 4 to 31 ng/mL in males and 2 to 21 ng/mL in females. Analyte stability has been demonstrated for at least 1.5 years from previously frozen samples. Details of NT-proBNP, C-reactive protein (CRP), and hs-cTnT have been previously described in CHS.

Covariates

Race, smoking status, and activity level and the presence of chronic lung disease were self-reported in the study. Coronary heart disease (CHD) was defined as having past myocardial infarction (MI), angina, or coronary revascularization. Echocardiographic parameters, including abnormal left ventricular ejection fraction (LVEF), left ventricular mass, and left atrial diameter, were determined using previously described methods.

Primary Outcomes

Primary longitudinal outcomes for this analysis were adjudicated cardiovascular death and new-onset (incident) HF. The methods of outcome ascertainment and adjudication in CHS have been described in detail previously. HF subtype was differentiated into HFrEF (LVEF ≥45%) or HFrEF (LVEF <45%) based on clinical echocardiograms or other cardiac imaging performed within 30 days of the HF event.

Statistical Analysis

CHS participants with available sST2 measurement without baseline HF were divided into quintiles based on sST2
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concentration for categorical analysis. sST2 was also analyzed as a continuous ln-transformed variable as well as a dichotomous variable using the FDA-approved cutoffpoint of 35 ng/mL. Demographics, traditional clinical cardiovascular risk factors, biochemical markers of inflammation, renal and cardiovascular disease, and echocardiographic imaging data were compared across quintiles using a 1-way ANOVA for continuous parametric variables and Kruskal–Wallis test for continuous nonparametric variables. Binary variables were compared across quintiles using the Pearson chi-square test. Cumulative incidence of HF and cardiovascular death in each category were calculated per 100 person-days using the Kaplan–Meier method and compared across sST2 quintiles using the log-rank test for trend. Multivariate analysis was performed by using Cox proportional hazard regression models. Demographic-, risk-factor-, and biomarker-adjusted (NT-proBNP) models were used to determine risk of incident HF, HFpEF, HFrEF, and cardiovascular death using previously validated models specific for HF35 and cardiovascular death.36 The HFrEF model also had correction for abnormal LVEF at baseline (estimated LVEF <55%). Sex, age, and race interaction were tested for each outcome. To determine the increase in model discrimination by adding sST2 to risk-factor–adjusted models, time-dependent Harrell C-statistics were calculated,37 with 95% CIs estimated with bootstrapping. Integrated discrimination index (IDI) and “category-free” net reclassification index (NRI) were calculated for the addition of sST2 to the models.38

SPSS software (version 22; IBM SPSS Statistics; IBM Corp, Armonk, NY) was used for the statistical analysis. NRI, C-statistic, and IDI estimates were generated using Stata software (version 12.1; StataCorp LP, College Station, TX).

Results

Participant Characteristics and Cross-Sectional Associations

There were 3915 participants with a measurable sST2 level also free of HF (Figure 1). Characteristics of those participants without sufficient stored serum for sST2 measurement (N=1698), compared to those with available serum for sST2 measurement, are shown in Table S1. The range of sST2 values was 4.5 to 179.3 ng/mL, with a median level of 23.5 ng/mL. Table 1 contains the baseline demographic and clinical characteristics of the CHS population divided by sST2 quintiles. Greater sST2 was associated with older age, male sex, and black race as well as risk factors for HF, such as CHD, diabetes mellitus, hypertension, increased body mass index, and low renal filtration function. Biomarkers of inflammation, fibrosis, cardiac stretch, and subclinical cardiovascular disease also significantly associated with sST2 levels across quintiles. Table 1 also describes the baseline echocardiographic characteristics of the population. Abnormal LVEF and greater left atrial diameter, but not LVM, were associated with higher sST2 levels. LV diastolic dimension was not different across men and was slightly smaller with progressively higher sST2 levels in women.

sST2 and Incident HF

There were 1185 incident HF events over a median follow-up of 11.7 years. Figure 2 shows the cumulative incidence of HF across quintiles of baseline sST2 levels with a significant difference across progressively higher quintiles (P<0.001). The incident rate per 100 patient-years was 2.06 in the lowest quintile compared to 3.71 in the highest sST2 quintile. Table 2 shows the association of sST2 with incident HF in both unadjusted and adjusted analyses. There was a significantly greater risk of incident HF with higher quintiles of sST2, with greater ln-transformed sST2 levels, and in elevated versus nonelevated sST2, using the FDA-based cutoff. These associations remained significant, though attenuated, in demographic and risk-factor–adjusted models. Additional adjustment for the cardiac specific biomarker, NT-proBNP, further reduced these associations; sST2 level was no longer associated with incident HF as a categorical or continuous variable, and with a modest, but still significant, 20% increase in risk for those with sST2 above the FDA-approve cut-off value of 35 ng/mL. The further addition of hs-cTnT to the model resulted in the dichotomous cutoff no longer being significant.

A total of 652 (55.0%) of incident HF cases could be classified as HFpEF (n=354; 54.3%) or HFrEF (n=298; 45.7%) cases based on imaging data near the time of diagnosis. The incidence rate of HFrEF increased across increasing quintiles of sST2 (Table 3; P<0.001); however, this trend was not significant with incident rates of HFpEF (P=0.07). As shown in Table 3, the highest quintile of sST2 was associated with incident HFpEF in unadjusted analysis (hazard ratio [HR], 1.46; 95% CI, 1.06–2.04), but this association was no longer significant after adjustment for clinical risk factors. Similarly, when sST2 was modeled as a continuous variable and using the cut-off value of 35 ng/mL, association with incident HFpEF was significant in unadjusted and demographic-adjusted models, but not when additionally adjusted for clinical risk factors. With respect to incident HFrEF, the point estimate with progressively higher quintiles of sST2 was larger than with incident HFpEF. However, also after adjustment for clinical risk factors, the association of sST2 with HFrEF was no longer significant irrespective of whether sST2 was evaluated by quintiles, as a continuous variable or at a dichotomous cutoff.

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Table 1. Baseline Characteristics Among Subjects Without Past HF by Quintile of Soluble ST2

| Variable                          | All       | Q1         | Q2         | Q3         | Q4         | Q5         | P Value |
|-----------------------------------|-----------|------------|------------|------------|------------|------------|---------|
| sST2 range, ng/mL                 | 3915      | <17.6      | 17.6 to 21.5 | 21.5 to 25.5 | 25.6 to 31.4 | >31.4      | <0.001  |
| Age (SD), y                       | 72.7 (5.5) | 71.6 (5.0) | 72.3 (5.3) | 72.6 (5.5) | 73.3 (5.8) | 73.7 (5.8) | <0.001  |
| Male (%)                          | 1601 (40.9)| 193 (24.7) | 255 (32.6) | 304 (38.8) | 385 (49.2) | 464 (59.3) | <0.001  |
| Black (%)                         | 664 (17.0) | 102 (13.0) | 134 (17.1) | 149 (19.0) | 128 (16.4) | 151 (19.3) | 0.006   |
| Hypertension (%)                  | 2322 (59.4)| 402 (5.15) | 442 (56.4) | 461 (59.0) | 490 (62.6) | 527 (67.4) | <0.001  |
| SBP, mm Hg                        | 133.4 (20.9)| 133.2 (21.1) | 138.1 (22.4) | 138.1 (21.1) | 139.6 (22.5) | 139.6 (22.5) | 0.001   |
| DBP, mm Hg                        | 71.1 (11.3) | 70.0 (10.9) | 70.5 (10.8) | 72.0 (11.8) | 71.4 (11.4) | 71.5 (11.5) | 0.003   |
| Diabetes mellitus (%)             | 693 (17.7) | 67.8 (12.5) | 137 (17.5) | 164 (21.0) | 227 (29.0) |            | <0.001  |
| Smoking (current/former) (%)      | 2069 (52.9)| 421 (53.8) | 390 (49.8) | 406 (51.9) | 424 (54.2) | 428 (54.7) | 0.277   |
| Body mass index, kg/m²            | 26.8 (4.7) | 26.2 (4.5) | 26.5 (4.5) | 27.4 (5.1) | 27.0 (4.7) | 26.9 (4.7) | 0.001   |
| Activity level, kcal/week         | 634 [140–1575] | 623 [158–1477] | 637 [140–1530] | 607 [140–1530] | 735 [203–1733] | 630 [113–1620] | 0.400   |
| CHD (%)                           | 684 (17.5) | 116 (14.8) | 126 (16.1) | 141 (18.0) | 138 (17.6) | 163 (20.8) | 0.002   |
| Chronic lung disease (%)          | 79 (2.0)   | 10 (1.3)   | 12 (1.5)   | 10 (1.3)   | 23 (2.9)   | 24 (3.1)   | 0.015   |
| HDL-c, mg/dL                      | 54.4 (15.8)| 56.8 (15.1)| 55.5 (15.4)| 55.1 (16.2)| 52.4 (15.2)| 52.5 (16.4)| <0.001  |
| LDL-c, mg/dL                      | 130.3 (35.1)| 133.4 (34.3)| 132.7 (34.2)| 130.8 (35.3) | 130.1 (35.4)| 124.5 (35.6)| <0.001  |
| NT-proBNP, pg/mL                  | 111.0 [56.8–219.8]| 88.7 [45.7–168.7]| 101.3 [55.0–187.5]| 120.8 [61.8–226.4]| 120.7 [59.5–237.4]| 133.7 [66.4–311.9]| <0.001  |
| hs-cTnT >3 ng/L (%)               | 2582 (66.0)| 418 (53.4)| 468 (59.8)| 498 (63.6)| 580 (74.1)| 618 (78.9)| <0.001  |
| hs-CRP*, mg/L                     | 2.50 [1.25–4.43]| 2.07 [1.11–3.64]| 2.31 [1.23–4.13]| 2.52 [1.23–4.38]| 2.69 [1.32–4.70]| 3.02 [1.47–6.46]| <0.001  |
| Galectin-3 >17.8 mg/L (%)         | 1224 (32.0)| 211 (27.8)| 241 (31.5)| 256 (33.1)| 246 (32.3)| 270 (35.2)| 0.037   |
| eGFR <60 mL/min per 1.73 m² (%)   | 836 (21.4)| 132 (17.9)| 148 (18.9)| 151 (19.3)| 202 (25.8)| 203 (25.9)| <0.001  |
| Cystatin C, mg/L                  | 1.04 [0.91–1.21]| 0.99 [0.88–1.14]| 1.03 [0.91–1.19]| 1.04 [0.92–1.19]| 1.06 [0.93–1.27]| 1.09 [0.95–1.31]| <0.001  |
| Abnormal LVEF (%)                 | 264 (7.8) | 41 (5.7)   | 36 (5.3)   | 33 (5.1)   | 64 (9.6)   | 70 (10.7)  | <0.001  |
| LVM, g (male)                     | 166.5 [139.3–204.0]| 178.1 [153.5–212.1]| 166.9 [140.6–204.2]| 164.5 [136.5–199.5]| 166.3 [137.9–207.9]| 160.8 [136.6–204.3]| 0.056   |
| LVM (male)                        | 86.5 [73.3–104.1]| 91.4 [78.7–109]| 86.8 [73.7–101]| 86.4 [70.1–104]| 85.5 [72.6–102]| 85.3 [71.9–104]| 0.115   |
| LVM, g (female)                   | 128.6 [108.5–154.4]| 128.5 [105.7–154.4]| 128.1 [109.3–151.4]| 126.7 [107.4–151.8]| 133.3 [107.7–158.9]| 129.1 [109.8–157.3]| 0.331   |
| LVM (female)                      | 75.0 [64.0–88.2]| 75.8 [64.8–90.5]| 74.8 [64.2–86.9]| 73.3 [62.4–86.9]| 76.2 [64.3–89.6]| 75.6 [64.5–91.7]| 0.179   |
| Left atrial diameter, cm          | 3.87 [0.66]| 3.78 [0.61]| 3.81 [0.64]| 3.87 [0.65]| 3.90 [0.69]| 3.95 [0.65]| <0.001  |

* hsCRP measured 3 years after sST2 in main cohort and in same study year as sST2 for supplemental (black) cohort.

† Abnormal LVEF defined as ejection fraction <55%.

‡ Among those with complete LVM measurement (N=2551).

CHD indicates coronary heart disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-c, high-density lipoprotein cholesterol; HF, heart failure; hs-cTnT, high-sensitivity troponin T; LDL-c, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; LVM, left ventricular mass; LVMI, left ventricular mass index; NT-proBNP, N-terminal pro–type B natriuretic peptide; SBP, systolic blood pressure.

Table 1 continues...
sST2 and Cardiovascular Mortality

There were a total of 1026 cardiovascular deaths over a median follow-up of 13.7 years. Figure 3 shows the Kaplan–Meier estimates of cardiovascular mortality across quintiles of baseline sST2 levels. The incidence of cardiovascular mortality was 1.48 per 100 person-years for the lowest quintile compared to 2.95 per 100 person-years for the highest quintile of sST2 \((P<0.001)\). The risk of cardiovascular mortality was significantly greater for greater quintiles of sST2, even after adjustment for clinical risk factors (Table 2), but this association was not significant after adjustment for NT-proBNP. Unlike the categorical analysis, sST2 remained a significant predictor when analyzed as a continuous variable and using the dichotomous cutoff of 35 ng/mL after adjustment for NT-proBNP level, but lost statistical significance with the addition of hs-cTnT.

Prediction Models

The addition of sST2 to the fully adjusted models resulted in only a modest, but significant, improvement in the C-statistic, IDI, and NRI, as shown in Table 4. Using the NRI, a net 6.7% of patients who developed cardiovascular death and 0.9% of patients who developed HF were correctly reclassified as higher risk and 7.2% and 4.6%, respectively, as lower risk when sST2 was added to the traditional risk factor models for each outcome.

Interaction Terms

As shown in Table 5, no interaction between sST2 (as continuous) and sex, race, and age was observed for cardiovascular death, all incident HF, HFrEF, or HFrEF in risk-factor–adjusted models, with the exception of a significant \((P=0.028)\) interaction between race and sST2 for incident HFrEF. sST2 was significantly associated with HFrEF among blacks (HR, 3.17; 95% CI, 1.47–6.85), but not among non–blacks (HR, 1.03; 95% CI, 0.72–1.46).

Discussion

Our study presents the impact of measuring sST2 levels for the prognostication of incident HF and cardiovascular death in a large community-dwelling cohort of older adults initially free of HF. Greater sST2 levels were associated with greater risk of incident HF and cardiovascular mortality after accounting for commonly measured risk factors, including comorbidities and demographics. However, unlike in younger general population cohorts, sST2 was not predictive of incident HF or cardiovascular mortality after adjustment for cardiac specific biomarkers. The addition of sST2 to demographics and clinical risk factors only modestly improved discrimination and risk reclassification for incident HF and cardiovascular death. However, similar to other cohorts, increasing levels of ST2 in older adults in a cross-sectional analysis were associated with higher risk demographics, increased comorbidities, and increasing levels of cardiac specific and noncardiac specific biomarkers that have been independently associated with poorer outcomes.\(^\text{16,27,28,39}\)

The association between sST2 and incident cardiovascular events has been examined in three general population cohorts previously: the Dallas Heart Study (DHS), FHS, and the FINRISK97 study.\(^\text{17,18,40}\) Compared to the CHS, the DHS cohort was significantly younger with a mean age of 43 years. In contrast to CHS, in DHS, only male sex and black race were associated with increasing quartiles of sST2. This may, in part, have been the result of a less-sensitive sST2 assay used in the DHS study.\(^\text{17}\) The presence of a strong association with black race with sST2 in both cohorts suggests a possible hereditary component to its expression. For the outcome of incident HF, our outcomes HRs were similar to the FHS. Statistical models presented by Wang et al. for ST2 in FHS also showed modest, yet significant, improvement in the C-statistic and net reclassification improvement.\(^\text{18}\) The loss of statistical significance of sST2 with the addition of the cardiac-specific biomarker, NT-proBNP, in the CHS cohort, compared to the retention of ST2 in multiple biomarker statistical models in the FHS cohort, might be explained by differences in the age distributions of the 2 cohorts. Whereas the CHS cohort had a much higher incidence of HF than the younger FHS participants, the lack of cardiac specificity of sST2 potentially limits its cardiovascular prognostic power given the increased prevalence of noncardiovascular inflammatory diseases that mediate sST2 levels in older participants.\(^\text{41}\) Further evidence also suggesting a lack of cardiac specificity of sST2 in middle-age adults.
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Table 2. Association of sST2 With Total Incident HF and Cardiovascular Mortality

| Incident HF | sST2 quintile | Unadjusted (N=3915) | Demographic Adjusted* (N=3915) | Risk-Factor Adjusted† (N=3886) | Risk-Factor+NT-proBNP Adjusted | Risk-Factor+NT-proBNP+hsTnT Adjusted |
|-------------|---------------|---------------------|---------------------------------|-------------------------------|-------------------------------|------------------------------------|
|             | Q1 (n=204)    | 2.06 (1.80–2.37)    | Reference                        | Reference                     | Reference                     | Reference                          |
|             | Q2 (n=216)    | 2.25 (1.97–2.57)    | 1.10 (0.91–1.33)                 | 1.04 (0.86–1.26)              | 0.97 (0.80–1.17)              | 0.93 (0.77–1.13)                   |
|             | Q3 (n=221)    | 2.47 (2.17–2.82)    | 1.22 (1.02–1.49)                 | 1.12 (0.93–1.36)              | 1.05 (0.87–1.28)              | 0.93 (0.77–1.13)                   |
|             | Q4 (n=269)    | 3.19 (2.83–3.60)    | 1.60 (1.33–1.92)                 | 1.36 (1.13–1.64)              | 1.21 (1.00–1.46)              | 1.05 (0.87–1.27)                   |
|             | Q5 (n=275)    | 3.71 (3.30–4.18)    | 1.91 (1.59–2.29)                 | 1.53 (1.27–1.85)              | 1.33 (1.10–1.61)              | 1.08 (0.89–1.31)                   |
|             | Test for trend |                      | P=0.001                          | P=0.001                       | P=0.001                       | P=0.183                           |
|             | ln(sST2)      |                      | 2.06 (1.75–2.43)                 | 1.68 (1.42–2.00)              | 1.46 (1.22–1.75)              | 1.19 (0.99–1.43)                   |
|             | sST2 >35 ng/mL |                      | 1.72 (1.47–2.02)                 | 1.46 (1.24–1.71)              | 1.36 (1.15–1.61)              | 1.20 (1.02–1.43)                   |

Cardiovascular death

| sST2 quintile | Unadjusted (N=3915) | Demographic Adjusted* (N=3915) | Risk-Factor Adjusted† (N=3886) | Risk-Factor+NT-proBNP Adjusted | Risk-Factor+NT-proBNP+hsTnT Adjusted |
|---------------|---------------------|---------------------------------|-------------------------------|-------------------------------|------------------------------------|
| Q1 (n=161)    | 1.48 (1.27–1.73)    | Reference                        | Reference                     | Reference                     | Reference                          |
| Q2 (n=161)    | 1.53 (1.31–1.79)    | 1.06 (0.85–1.32)                 | 0.99 (0.79–1.23)              | 0.96 (0.77–1.19)              | 0.91 (0.73–1.13)                   |
| Q3 (n=218)    | 2.23 (1.95–2.54)    | 1.58 (1.29–1.94)                 | 1.41 (1.15–1.74)              | 1.26 (1.02–1.55)              | 1.10 (0.90–1.36)                   |
| Q4 (n=236)    | 2.49 (2.19–2.83)    | 1.79 (1.46–2.18)                 | 1.44 (1.17–1.76)              | 1.23 (1.00–1.51)              | 1.09 (0.88–1.34)                   |
| Q5 (n=250)    | 2.95 (2.60–3.34)    | 2.20 (1.80–2.68)                 | 1.66 (1.35–2.04)              | 1.40 (1.13–1.72)              | 1.15 (0.93–1.42)                   |
| Test for trend | P=0.001            | P=0.001                          | P=0.001                       | P=0.001                       | P=0.062                           |
| ln(sST2)      | 2.34 (1.97–2.78)    | 1.80 (1.50–2.16)                 | 1.51 (1.25–1.83)              | 1.24 (1.02–1.50)              | 1.18 (0.95–1.48)                   |
| sST2 >35 ng/mL | 1.87 (1.59–2.20)    | 1.49 (1.26–1.77)                 | 1.36 (1.15–1.61)              | 1.21 (1.02–1.44)              | 1.18 (0.97–1.43)                   |

HF indicates heart failure; sST2, soluble ST2.
*Demographic adjusted: adjusted for age, sex, and race.
†Risk-factor adjusted: for incident HF, adjusted for demographics and history of coronary heart disease, smoking status, systolic blood pressure, heart rate, serum glucose, creatinine, albumin levels, and left ventricular hypertrophy by electrocardiogram. For cardiovascular death, adjusted for demographics and history of coronary heart disease, diabetes mellitus, use of antihypertensive medications, total cholesterol, and high-density lipoprotein cholesterol.

was found on a subsequent analysis of the FHS cohort for structural heart disease, which found that sST2 levels did not discriminate between individuals with or without left ventricular hypertrophy (LVH) and depressed left ventricular systolic function.42 Last, it is notable that our results differed somewhat from the much younger, less racially heterogeneous FINRISK97 cohort, which did not show significant cardiovascular outcomes (AMI, CHD, stroke, and HF) with minimal changes in the point estimates of risk with increasing sST2 levels, even when adjusting for only the Framingham risk factors. Ultimately, the conclusion of that study was similar, that sST2 level was not an independent predictor of incident HF.50

No previous studies in community-based cohorts have examined the relative prognostic importance of sST2 in predicting the incidence of HFpEF versus HFrEF. Preliminary cross-sectional data in hypertensive patients suggested that sST2 levels could differentiate HFpEF from asymptomatic hypertension.26 We anticipated that sST2 could be a stronger prognostic factor for HFpEF than HFrEF, given that it has been hypothesized that HFpEF patients develop HF as a result of the overall burden of noncardiovascular comorbidities.43 sST2 levels may serve as a summation of the burden of comorbidities that contribute to HFpEF, particularly those observed in older adults. However, although the point estimates of associations were slightly higher for HFrEF than HFpEF, neither association was significant in risk-factor–adjusted models. This may have been attributed to a smaller number of events for these HF subtypes. Overall, however, our study suggests there is modest prognostic utility of sST2 when predicting incident HF of all types in an ambulatory population of older adults.

Limitations

There are several limitations to our study. sST2 has a low cardiac specificity and can be elevated in numerous other conditions, such as autoimmune diseases (systemic lupus
erythematous, rheumatoid arthritis, and granulomatosis with polyangiitis,44 asthma,45 liver failure,46 sepsis,47 and other pulmonary diseases,48,49 which were not specifically recorded in the CHS database. As a result, noncardiovascular comorbidity could not be completely ascertained with our study. Though we were able to differentiate incident HF phenotype in 55% of the subjects, we cannot exclude that the absence of imaging phenotype in the remaining 45% may have biased our findings and reduced our ability to determine whether sST2 could selectively more accurately predict HFpEF.

Table 3. Association of sST2 With Incident HFpEF and HFrEF

| sST2 quintile | Incidence (Per 100 Patient-Years) | Unadjusted (N=3915) | Demographic-Adjusted (N=3915) | Risk-Factor Adjusted (N=3886) | Risk-Factor+NT-proBNP Adjusted |
|---------------|----------------------------------|------------------|-------------------------------|--------------------------------|-------------------------------|
| HFpEF (n=354 events) |  |  |  |  |  |
| Q1 (n=73) | 0.74 (0.59–0.93) | Reference | Reference | Reference | Reference |
| Q2 (n=66) | 0.69 (0.54–0.88) | 0.95 (0.68–1.33) | 0.93 (0.67–1.30) | 0.87 (0.63–1.22) | 0.85 (0.61–1.19) |
| Q3 (n=70) | 0.78 (0.62–0.99) | 1.12 (0.80–1.55) | 1.08 (0.78–1.50) | 1.04 (0.75–1.45) | 0.95 (0.68–1.33) |
| Q4 (n=73) | 0.87 (0.69–1.09) | 1.26 (0.91–1.74) | 1.18 (0.85–1.64) | 1.08 (0.77–1.51) | 0.98 (0.70–1.38) |
| Q5 (n=72) | 0.97 (0.77–1.23) | 1.46 (1.06–2.04) | 1.34 (0.96–1.88) | 1.19 (0.84–1.68) | 1.02 (0.72–1.46) |
| Test for trend | \(P=0.07\) | \(P=0.006\) | \(P=0.036\) | \(P=0.173\) | \(P=0.652\) |
| ln(sST2) | 1.54 (1.13–2.08) | 1.42 (1.04–1.95) | 1.25 (0.96–1.68) | 1.19 (0.84–1.46) | 1.02 (0.72–1.46) |
| sST2 >35 ng/mL | 1.52 (1.12–2.07) | 1.42 (1.04–1.94) | 1.27 (0.92–1.75) | 1.14 (0.82–1.59) |  |

| HFrEF (n=298 events) |  |  |  |  |  |
| sST2 quintile |  |  |  |  |  |
| Q1 (n=44) | 0.45 (0.33–0.60) | Reference | Reference | Reference | Reference |
| Q2 (n=61) | 0.64 (0.49–0.82) | 1.43 (0.97–2.11) | 1.32 (0.89–1.94) | 1.20 (0.81–1.78) | 1.19 (0.81–1.76) |
| Q3 (n=49) | 0.55 (0.41–0.73) | 1.25 (0.83–1.87) | 1.06 (0.71–1.60) | 0.97 (0.64–1.47) | 0.86 (0.57–1.30) |
| Q4 (n=67) | 0.80 (0.63–1.01) | 1.82 (1.24–2.66) | 1.38 (0.93–2.02) | 1.17 (0.79–1.73) | 1.00 (0.68–1.48) |
| Q5 (n=77) | 1.04 (0.83–1.30) | 2.42 (1.67–3.50) | 1.68 (1.14–2.45) | 1.39 (0.94–2.06) | 1.07 (0.72–1.59) |
| Test for trend | \(P=0.001\) | \(P=0.001\) | \(P=0.011\) | \(P=0.143\) | \(P=0.949\) |
| ln(sST2) | 2.18 (1.58–3.02) | 1.52 (1.08–2.13) | 1.24 (0.85–1.80) | 0.94 (0.66–1.34) |  |
| sST2 >35 ng/mL | 1.93 (1.43–2.61) | 1.50 (1.10–2.03) | 1.38 (0.98–1.93) | 1.16 (0.85–1.59) |  |

HFpEF indicates heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; sST2, soluble ST2.

Table 4. Risk Prediction Models (C Statistic, IDI, NRI)

|  | Cardiovascular Death | HF |
|---|---|---|
| C statistic | 0.736 | 0.713 |
| Clinical model | 0.740 | 0.715 |
| Clinical model+sST2 | Change in AUC | 0.004 | 0.002 |
| P value | 0.003 | 0.001 |
| Event NRI (95% CI) | 6.72 (–0.56, 14.88) | 0.93 (–3.58, 5.15) |
| Nonevent NRI (95% CI) | 7.22 (3.19, 8.84) | 4.56 (–0.08, 8.98) |
| IDI | 0.0041 (\(P=0.004\)) | 0.0032 (\(P=0.018\)) |

AUC indicates area under the curve; HF, heart failure; IDI, integrated discrimination improvement; NRI, net reclassification index; sST2, soluble ST2.

Figure 3. Cumulative incidence of cardiovascular death. CV indicates cardiovascular.
Table 5. Sex/Race/Age Interaction Terms (P Values)

|                | Cardiovascular Death | HF | HFpEF | HFrEF |
|----------------|----------------------|----|-------|-------|
| Sex            | 0.115                | 0.282 | 0.954 | 0.196 |
| Race           | 0.061                | 0.198 | 0.028 | 0.799 |
| Age*           | 0.512                | 0.286 | 0.204 | 0.839 |

HF indicates heart failure; HFpEF heart failure with preserved ejection fraction; HFrEF heart failure with reduced ejection fraction.

*Age interaction term computed as (age−mean[age])×(lnST2−mean[lnST2]).

versus HFrEF. Sufficient stored serum for sST2 measurement was unavailable for a substantial minority of participants, which may have biased the observed associations. Furthermore, the CHS samples had been frozen for approximately 18 years before measurement and had undergone previous freeze thaw. The longest published data for retesting frozen samples is 18 months, and no appreciable change in sST2 values was noted compared to the baseline unfrozen samples. In the Framingham study, sST2 was an independent predictor of death and HF, suggesting that our findings were more the result of the population tested and less likely an issue of analyte stability, though we cannot exclude that additional years of freezing and previous freeze thaws may have degraded sST2 and diminished differences between patients with and without adverse outcomes.

Conclusions

Our study suggests limitations of sST2 concentrations as an independent predictor for incident HF in community-dwelling older adults despite strong cross-sectional associations with cardiac pathology and risk factors.

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**Table S1.** Characteristics of Participants with Missing and Non-Missing sST2 at baseline, among those without Prevalent HF.

| Characteristic                              | Missing sST2 (n=1698) | Non-missing sST2 (n=3915) | p-value |
|---------------------------------------------|-----------------------|---------------------------|---------|
| Age (years)                                 | 72.8 (5.6)            | 72.7 (5.5)                | 0.5     |
| Male                                        | 44.8%                 | 40.9%                     | .006    |
| African-American                           | 11.8%                 | 17.0%                     | <.001   |
| Hypertension                               | 56.1%                 | 59.4%                     | .02     |
| SBP (mmHg)                                  | 135.9 (21.4)          | 136.9 (21.7)              | 0.1     |
| DBP (mmHg)                                  | 70.6 (11.4)           | 71.1 (11.3)               | 0.2     |
| Diabetes                                    | 10.8%                 | 17.7%                     | <.001   |
| Smoking (current / former)                  | 55.1%                 | 52.9%                     | 0.1     |
| Body mass index (kg/m²)                     | 26.5 (4.6)            | 26.8 (4.7)                | .046    |
| Activity level (kcal/week)                  | 712 [180, 1610]       | 634 [140, 1575]           | 0.1     |
| Coronary Heart Disease                      | 17.4%                 | 17.5%                     | 0.9     |
| Chronic lung disease                        | 2.6%                  | 2.0%                      | 0.2     |
| HDL-c, mg/dL                                | 54.5 (15.8)           | 54.4 (15.8)               | 0.9     |
| LDL-c, mg/dL                                | 130.5 (36.8)          | 130.3 (35.1)              | 0.9     |
| Abnormal LVEF                               | 7.8%                  | 7.8%                      | 0.9     |