CLINICAL RESEARCH STUDY

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Prognostic Value of Soluble ST2 After Myocardial Infarction: A Community Perspective

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ABSTRACT

BACKGROUND: Soluble ST2 (sST2) is a marker of cardiac mechanical strain hypothesized to adversely impact short-term prognosis after myocardial infarction. We examined the association of sST2 with longer-term outcomes after myocardial infarction in a geographically defined community.

METHODS: Olmsted County, Minnesota residents who experienced an incident (first-ever) myocardial infarction between November 1, 2002 and December 31, 2012 were prospectively enrolled; sST2 levels were measured. Patients were followed for heart failure and death.

RESULTS: We studied 1401 patients with incident myocardial infarction (mean age 67 years; 61% men; 79% non-ST-elevation myocardial infarction). Median sST2 (ng/mL) was 48.7 (25^{th}-75^{th} percentile 32.5-103.3). Soluble ST2 was elevated in 51% of patients. Higher values of sST2 were associated with increased age, female sex, and comorbidities. During 5 years of follow-up, 388 persons died and 360 developed heart failure. After adjustment for age, sex, comorbidities, Killip class, and troponin T, the hazard ratios for death were 1.73 (95% confidence interval [CI], 1.22-2.45) and 3.57 (95% CI, 2.57-4.96) for sST2 tertiles 2 and 3, respectively (P_{trend} <.001). For heart failure, the hazard ratios were 1.67 (95% CI, 1.18-2.37) and 2.88 (95% CI, 2.05-4.05), respectively (P_{trend} <.001). Results were similar among 30-day survivors.

CONCLUSIONS: In the community, sST2 elevation is present in half of myocardial infarctions. Higher values of sST2 are associated with a large excess risk of death and heart failure independently of other prognostic indicators. Measurement of sST2 should be considered for risk stratification after myocardial infarction.

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KEYWORDS: Heart failure; Mortality; Myocardial infarction; Soluble ST2

Over 1 million people suffer a myocardial infarction each year in the US.[1] With improved treatment, more patients survive, resulting in an increased pool of candidates for ventricular remodeling and heart failure post myocardial infarction.[2] Importantly, as clinical presentation is changing with decreasing incidence of ST-elevation myocardial infarction[3] and increasing age of the patients, approaches to risk stratification must also evolve. Within this context, it is critical to evaluate the prognostic value of novel markers of outcome. Soluble suppression of tumorigenicity-2 (sST2), a member of the interleukin (IL)-1 receptor family, has been implicated in experimental studies as a marker of cardiac mechanical strain, which may predict ventricular remodeling. In acute myocardial infarction, clinical trials data suggest that elevated sST2 is associated with adverse outcomes in the short term.[4,5] However, we do not know if these findings are broadly generalizable to all patients with myocardial infarction rather than applicable to selected trial participants. Further, it is not known if sST2 also predicts

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longer-term outcomes. Addressing these gaps in knowledge in a large community cohort with long-term follow-up is needed before the use of sST2 in clinical practice can be considered.

Thus, within a prospective longitudinal community cohort of persons with incident myocardial infarction, we examined the association of sST2 measurement with the long- term occurrence of heart failure and death post myocardial infarction.

CLINICAL SIGNIFICANCE

- Soluble ST2 is elevated in half of patients following an incident myocardial infarction.
- Soluble ST2 is associated with risk of death and heart failure over a long period of follow-up.
- Our results support measuring soluble ST2 in the evaluation of clinical risk following myocardial infarction.

METHODS

Study Setting

This prospective community surveillance study was conducted in Olmsted County, Minnesota and utilized the resources of the Rochester Epidemiology Project. The Rochester Epidemiology Project is a medical records linkage system that links and archives the medical records of nearly all persons living in the county.[6] All medical diagnoses are maintained through an electronic index, and patients can be identified through their in- and outpatient contacts across the local medical providers.[7] This study was approved by the appropriate institutional review boards.

Identification of the Myocardial Infarction Patients

All Olmsted County residents admitted to Mayo Clinic hospitals in Rochester, Minnesota between November 1, 2002 and December 31, 2012 with a cardiac troponin T level of 0.03 ng/mL or higher were identified within 12 hours of the blood draw. Written consent was obtained from all patients or next of kin. Samples were stored for future biomarker measurements.

As previously described,[8] the validation of myocardial infarction relied on standard algorithms integrating cardiac pain, electrocardiogram (ECG), and biomarker data. According to current guidelines, each case was classified by troponin T.[9] In clinical practice, serial troponin T measurements were performed after infarction onset. The presence or absence of a change (rise or fall) between any 2 measurements was defined by a difference of at least 0.05 ng/mL, which is greater than the level of imprecision of the assay at all concentrations.[9] Circumstances that might invalidate biomarker values were recorded.[10] Troponin T was measured with a sandwich electrochemiluminescence immunoassay on the Elecsys 2010 (Roche Diagnostics Corporation; Indianapolis, Ind) in the laboratories of the Department of Laboratory Medicine and Pathology.

Up to 3 ECGs per episode were coded using the Minnesota Code Modular ECG Analysis System.[11] According to the algorithm, myocardial infarctions were classified as definite, probable, suspect, or no infarction.[12,13] In the current study, myocardial infarction was defined as an incident (first-ever) definite or probable myocardial infarction.

Soluble ST2 Measurement

Soluble ST2 was measured from stored plasma samples using a high-sensitivity sandwich monoclonal immunoassay (Presage ST2 assay; Critical Diagnostics, San Diego, Calif.). The antibodies used in the Presage assay were generated from a recombinant protein based upon the human cDNA clone for the complete soluble sequence.[14] This platform offers improved accuracy in quantifying sST2 levels, particularly at lower concentrations. This specific assay has high sensitivity; the reliability of running the Presage ST2 assay on ethylenediaminetetraacetic acid plasma samples stored at −70°C (as per biomarker core lab) has been established in numerous studies.[15-17] Calibration and standardization of this assay were performed according to the manufacturer's protocol. Previous reports document the intra- and interassay coefficients of variation as <2.5% and <4.0%, respectively.[14]

Ascertainment of Other Clinical Characteristics

Demographic and clinical characteristics at the time of the infarction were collected from the medical records. Clinicians' diagnoses were used to define the comorbidities measured by the Charlson index.[18] Estimated glomerular filtration rate was calculated using the creatinine value closest to myocardial infarction diagnosis (± 1 year) with the Modification of Diet in Renal Disease Study equation.[19] Body mass index (kg/m^2) was calculated using height and weight at the time of the myocardial infarction event.

The severity of the myocardial infarction was evaluated using several indicators.[3] Killip class served as the indicator of hemodynamic severity on admission.[20] The presence of ST-segment elevation and Q waves was ascertained using the Minnesota code of the ECG.[11] Reperfusion or revascularization (percutaneous coronary intervention, coronary artery bypass graft, and thrombolysis) during the myocardial infarction hospitalization was collected from the medical records.

Outcome Ascertainment

Participants were followed for heart failure and death through December 31, 2014. For heart failure, participants with International Classification of Diseases, Ninth Revision, Clinical Modification code 428 at any time during

follow-up were identified, and abstractors reviewed the records to validate heart failure using the Framingham criteria.[21] This approach affords high feasibility and excellent interobserver agreement.[22] Deaths were obtained from inpatient and outpatient medical records as well as death certificates, which are received from Olmsted County and the state of Minnesota.

Statistical Analysis

Data are presented as frequencies (percent), mean (SD), or median (25^{th}-75^{th} percentile), as appropriate. Published normal values from the Framingham Heart Study were used for normal referent ranges for sST2 levels.[23] Soluble ST2 was categorized as elevated if the values (ng/mL) were above the 99^{th} percentile stratified by age and sex: *females*, ≤44 years: 29.5; 45-54 years: 34.0; 55-64 years: 39.3; ≥65 years: 45.3; *males*, ≤44 years: 46.7; 45-54 years: 48.7; 55-64 years: 50.8; ≥65 years: 53.0. To examine a dose−response relationship between sST2 and outcomes, tertiles of sST2 were analyzed and defined as tertile 1: 0 < sST2 ≤37 ng/mL, tertile 2: 37 < sST2 ≤72.3 ng/mL, and tertile 3: sST2 >72.3 ng/mL. Clinical characteristics were compared according to tertiles of sST2, with the Mantel-Haenszel chi-squared test for categorical variables or linear regression for continuous variables.

Survival after myocardial infarction was assessed with the Kaplan-Meier method according to sST2 tertiles and compared with the log-rank test. The cumulative incidence of heart failure after myocardial infarction was estimated according to the tertiles of sST2, treating death as a competing risk. The associations between sST2 tertiles and death and heart failure were assessed using Cox proportional hazards regression. Follow-up was truncated at 5 years; thereafter, the proportional hazards assumption, tested using the scaled Schoenfeld residuals, showed evidence of being violated with a reduction in the relative hazards. Hazard ratios (HR) were estimated using the lowest tertile as the referent in unadjusted models and models adjusted for age, sex, Charlson comorbidity index, Killip class >1, and the maximum of the troponin T measurements. In models predicting death, heart failure was included as a time-dependent covariate, while models predicting heart failure also adjusted for heart failure prior to the myocardial infarction. All models were further adjusted for time from symptom onset to sST2 measurement and for reperfusion or revascularization during the hospitalization for the index myocardial infarction. All analyses were repeated among 30-day survivors. All analyses were performed using SAS statistical software, version 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

A total of 1401 patients with incident myocardial infarction between November 2002 and December 2012 and stored samples for sST2 measurement were included in the study. The mean (SD) age was 67.3 (14.9) years, 61% were male, and 79% presented with non-ST-elevation myocardial infarction. The median sST2 value (ng/mL) was 49 (25th-75th percentiles, 33-104); 720 patients (51%) were considered to have elevated sST2, compared with published normal values.[23]

Higher values of sST2 were associated with increased age, female sex, and comorbidities (**Table 1**). Patients with higher sST2 values were more likely to have Q waves on the ECG, anterior myocardial infarction, and Killip class >1. During the first 5 years of follow-up (mean follow-up of 3.6 [SD 1.8] years), 388 (27.7%) patients died (47 in sST2 tertile 1, 110 in tertile 2, and 231 in tertile 3). Higher sST2 values were associated with markedly increased mortality (**Figure 1A**) as, at 5 years, mortality was 11.8% (95% confidence interval [CI], 8.5%-14.9%), 25.5% (95% CI, 21.2%-29.5%), and 52.0% (95% CI, 47.0%-56.5%) for patients with sST2 values in tertiles 1, 2, and 3, respectively. This large excess mortality equated to nearly a 2.5-fold increased risk of death for patients with sST2 values in tertile 2 (unadjusted HR 2.49; 95% CI, 1.77-3.50) and more than a sixfold increased risk of death for patients with sST2 values in the third tertile (unadjusted HR 6.75; 95% CI, 4.93-9.24, P_{trend} <.001; **Table 2**). This large excess risk of death was only partially attenuated by adjustment for age, sex, comorbidity, Killip class, and maximum troponin T; higher sST2 values were still independently associated with risk of death (HR 1.73 [95% CI, 1.22-2.45] and HR 3.57 [95% CI, 2.57-4.96] for sST2 tertile 2 and 3, respectively; P_{trend} <.001). Further adjustment for time to sST2 measurement, heart failure as a time-dependent variable, or acute reperfusion/revascularization did not materially alter the results.

During the 5 years of follow-up, 360 (25.7%) subjects developed heart failure (48 in sST2 tertile 1, 107 in tertile 2, and 205 in tertile 3). The occurrence of heart failure was higher among patients with higher sST2 values (**Figure 1B**). At 5 years, the cumulative incidence of heart failure, treating death as a competing risk, was 11.4% (95% CI, 8.1%-15.2%), 23.6% (95% CI, 20.0%-27.5%), and 44.8% (95% CI, 39.6%-48.7%) for patients with sST2 values in tertiles 1, 2, and 3, respectively. Patients with sST2 values in tertile 2 had a 2.5-fold greater risk of heart failure (unadjusted HR 2.49; 95% CI, 1.77-3.50, P_{trend} <.001; **Table 2**), while those with sST2 values in tertile 3 had more than a sixfold increased risk of heart failure (unadjusted heart failure 6.58; 95% CI, 4.80-9.03, P_{trend} <.001). Increased risk of heart failure persisted after adjustment for age, sex, Charlson comorbidity index, Killip class, maximum troponin T, and heart failure prior to the myocardial infarction (HR 1.67; 95% CI, 1.18-2.37 and HR 2.88; 95% CI, 2.05-4.05 for sST2 tertile 2 and 3, respectively; P_{trend} <.001). The results were similar after further adjustment for time to sST2 measurement or acute reperfusion/revascularization.

All analyses were then restricted to the 1322 patients who survived at least 30 days after the index myocardial infarction.

Table 1 Clinical Characteristics of Incident Myocardial Infarction Patients by Tertiles of Soluble ST2

	Tertile 1 (N = 467)	Tertile 2 (N = 467)	Tertile 3 (N = 467)	*P*-Value
Age (y), mean (SD)	63.4 (13.7)	66.5 (15.2)	72.1 (14.6)	<.001
Male sex	318 (68.1)	290 (62.1)	245 (52.5)	<.001
Cardiovascular risk factors				
Body mass index, mean (SD)	29.8 (6.1)	29.2 (6.5)	27.8 (6.9)	<.001
Current smoker	105 (22.5)	97 (20.8)	78 (16.7)	.076
Familial coronary disease	120 (25.8)	103 (22.2)	66 (14.3)	<.001
Diabetes mellitus	88 (18.8)	118 (25.3)	129 (27.6)	.005
Hypertension	313 (67.0)	325 (69.6)	355 (76.0)	.008
Hyperlipidemia	318 (68.1)	308 (66.0)	300 (64.2)	.460
Comorbidities				
Prior heart failure	21 (4.5)	56 (12.0)	102 (21.8)	<.001
Cerebrovascular disease	35 (7.5)	70 (15.0)	84 (18.0)	<.001
History of malignancy	66 (14.1)	87 (18.6)	116 (24.8)	<.001
Chronic obstructive pulmonary disease	43 (9.2)	73 (15.6)	111 (23.8)	<.001
eGFR (mL/min per 1.73 m^2), median (25th-75th percentile)	65.3 (54.7-77.6)	60.2 (48.1-73.9)	56.2 (42.0-70.3)	<.001
Charlson comorbidity index, median (25th-75th percentile)	0.0 (0.0-2.0)	1.0 (0.0-3.0)	2.0 (1.0-4.0)	<.001
MI characteristics				
Maximum troponin T (ng/mL), median (25th-75th percentile)	0.5 (0.2-1.4)	0.8 (0.2-2.8)	0.6 (0.2-2.2)	.039
Non ST-elevation MI	372 (79.7)	356 (76.2)	382 (81.8)	.107
Q waves on ECG	171 (40.3)	236 (54.6)	279 (64.3)	<.001
Anterior MI	117 (25.1)	164 (35.1)	222 (47.5)	<.001
Killip class >1	46 (10.0)	99 (21.5)	170 (36.9)	<.001

Data are presented as N (%) unless otherwise specified.
ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; MI = myocardial infarction.

During follow-up, 311 (23.5%) of the 30-day survivors died and 333 (25.2%) developed heart failure. Patients with higher values of sST2 experienced a large increased risk of death (Figure 2A, Table 2). This excess risk was only marginally attenuated after adjustment for age, sex, comorbidity index, Killip class, and maximum troponin T. Indeed, sST2 values in tertiles 2 and 3 conferred an independent 1.7-fold (HR 1.74; 95% CI, 1.22-2.50) and nearly a threefold increased risk

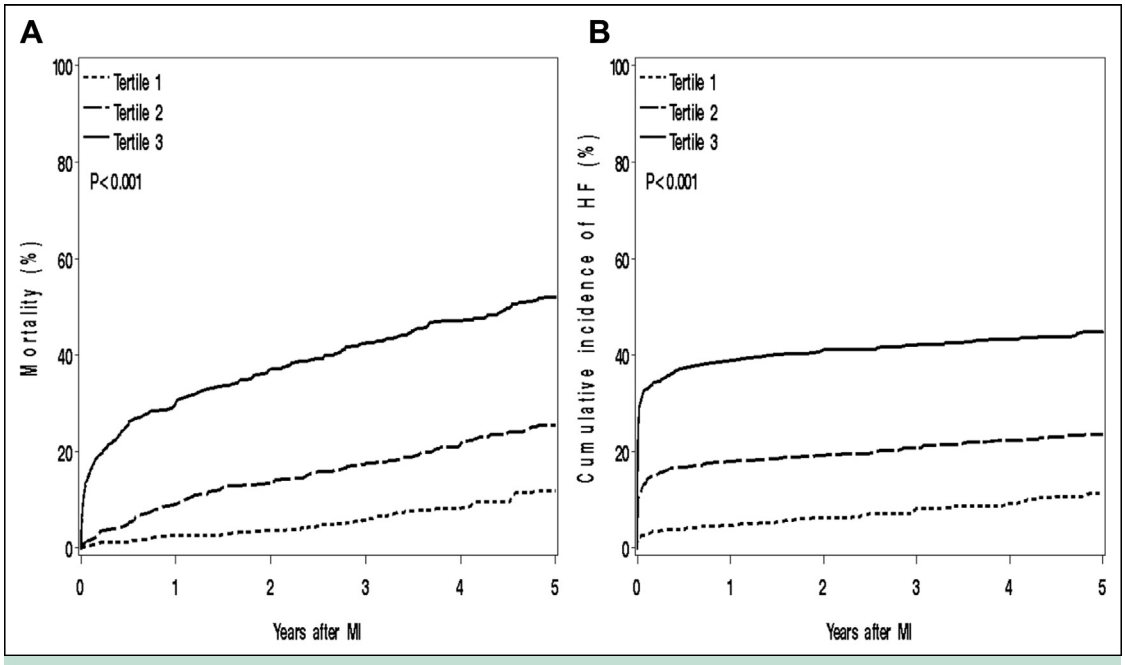

Figure 1 Cumulative incidence of all-cause mortality (**A**) and heart failure (**B**) by tertiles of soluble ST2 within the first 5 years following incident myocardial infarction (MI).

Table 2 Hazard Ratios (95% Confidence Intervals) Associated with Tertiles of Soluble ST2 for All-Cause Death and Heart Failure After Myocardial Infarction, Overall Within the First 5 Years of Follow-Up and Among 30-Day Survivors

	Tertile 1 N = 467	Tertile 2 N = 467	Tertile 3 N = 467	P_{trend}
Overall (n = 1401)				
Death (n = 388)				
Unadjusted	1.0	2.49 (1.77-3.50)	6.75 (4.93-9.24)	<.001
Adjusted*	1.0	1.73 (1.22-2.45)	3.57 (2.57-4.96)	<.001
HF (n = 360)				
Unadjusted	1.0	2.49 (1.77-3.50)	6.58 (4.80-9.03)	<.001
Adjusted†	1.0	1.67 (1.18-2.37)	2.88 (2.05-4.05)	<.001
Among 30-day survivors (n = 1322)				
Death (n = 311)				
Unadjusted	1.0	2.46 (1.73-3.49)	5.26 (3.78-7.31)	<.001
Adjusted*	1.0	1.74 (1.22-2.50)	2.94 (2.08-4.16)	<.001
HF (n = 333)				
Unadjusted	1.0	2.47 (1.75-3.48)	6.54 (4.74-9.02)	<.001
Adjusted†	1.0	1.67 (1.17-2.37)	2.98 (2.11-4.22)	<.001

*Model for death is adjusted for age, sex, Charlson comorbidity index, Killip class, and maximum troponin T.
†Model for heart failure (HF) is adjusted for age, sex, Charlson comorbidity index, Killip class, maximum troponin T, and HF prior to the myocardial infarction.

of death (HR 2.94; 95% CI, 2.08-4.16), respectively (P_{trend} <.001). Similarly, the risk of heart failure after myocardial infarction was greater with higher values of sST2 and with death treated as a competing risk (Figure 2B, Table 2). After adjustment for age, sex, Charlson comorbidity index, Killip class, maximum troponin T, and heart failure prior to the myocardial infarction, sST2 values in tertiles 2 and 3 still conferred nearly a 1.7-fold (HR 1.67; 95% CI, 1.17-2.37) and a threefold (HR 2.98; 95% CI, 2.11-4.22) increase in the risk of heart failure, respectively (P_{trend} <.001).

DISCUSSION

To the best of our knowledge, we report herein on the largest community study to date, which evaluated, among incident myocardial infarction, the frequency of sST2 elevation, its clinical correlates, and its prognostic value.

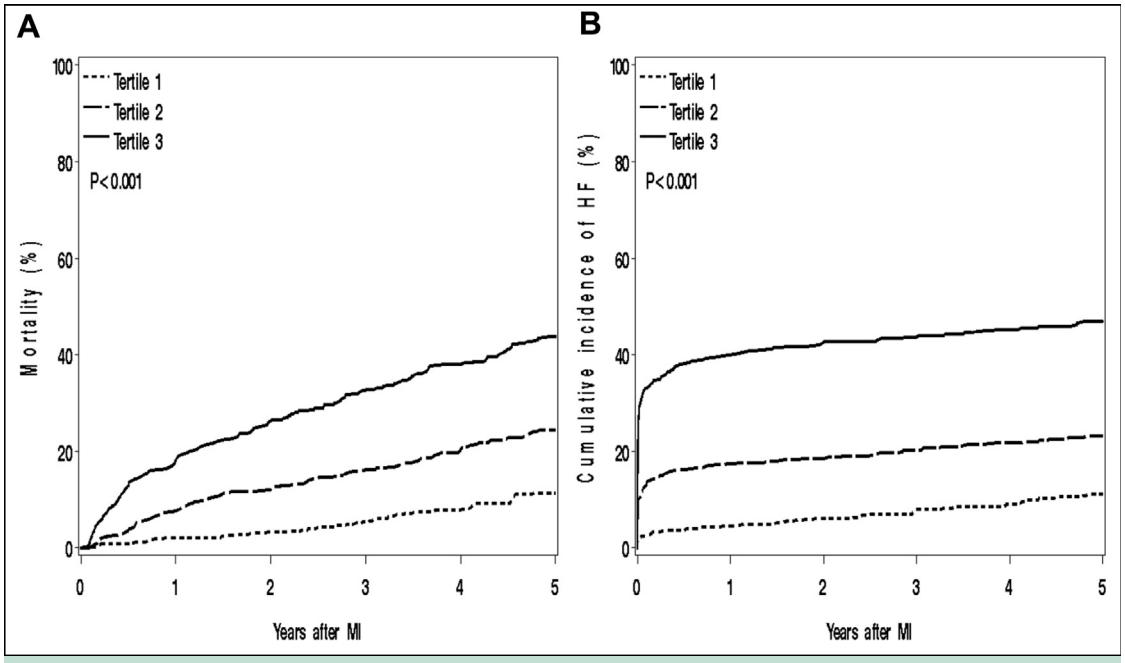

Figure 2 Cumulative incidence of (**A**) all-cause mortality and (**B**) heart failure (HF) by tertiles of soluble ST2 within the first 5 years following incident myocardial infarction (MI) among 30-day survivors.

Our findings that, in a nonselected geographically defined cohort, sST2 is elevated in more than half of the patients presenting with an incident myocardial infarction, were unexpected. The substantial increase in the risk of death and heart failure with increasing levels of sST2 was striking, as it was independent of indicators of myocardial infarction severity and of comorbidity. The dose–response pattern uncovered by the tertile analyses supports causality. Because these data represent the comprehensive experience of a community, they are of optimal clinical relevance and draw attention to the role that sST2 could play in contemporary risk stratification after myocardial infarction in clinical practice.

Soluble ST2 is a member of the IL-1 receptor family that has been implicated in the development of myocardial fibrosis and remodeling. Expressed by cardiomyocytes and cardiac fibroblasts, an excess of soluble circulating sST2 leads to the binding and subsequent reduced bioavailability of the circulating cardioprotective ligand IL-33 that reduces myocardial fibrosis, prevents cardiomyocyte hypertrophy, reduces apoptosis, and improves myocardial function.[24,25] In animal models, excess levels of sST2 in the context of left ventricular pressure and volume overload is associated with myocardial hypertrophy, dilation of ventricular chambers, and reduction in ejection fraction.[25,26] In previous clinical reports, sST2 levels were only weakly correlated with determinants of infarct severity and prognostic indicators including ejection fraction, comorbidity, N-terminal pro B-type natriuretic peptide, C-reactive protein, and cardiac troponin. Herein, we report that subjects with higher sST2 values had a higher Killip class, but that there was only a weak association between sST2 tertiles and maximum troponin T and none with ST elevation status ($P = .36$, data not shown). The present findings thus emphasize the limited link between sST2 and other clinical characteristics of myocardial infarction, and support the contention that sST2 elevation reflects mechanistic pathways distinct from those assessed by established biomarkers.[27] Thus, as a novel marker, sST2 has the potential for providing new prognostic information. The role of sST2 as an indicator of adverse events has been reported[4,5,28] in post hoc analyses of clinical trials.[4,5] However, these reports relied on different types of assays and heterogeneous diagnoses. Most importantly, their inherent selection biases limit external validity. Finally, follow-up did not exceed 1 year, and in most cases was substantially shorter. Thus, the long-term prognostic value of sST2 remained undefined. Our study substantially augments existing knowledge by demonstrating in a large geographically defined cohort of unselected community patients with validated diagnoses of myocardial infarction that sST2 elevation is associated in a dose–response fashion with a large short- and long-term excess risk of death and heart failure. This strong association remained independently of other commonly used indicators of risk after infarction and independent of comorbidity. The present results from a community cohort are important, as by design, they are most closely reflective of everyday clinical practice.

These findings are also timely. Indeed, it is important to remember that, over the past decade, major changes in the epidemiology of myocardial infarction have been reported in multiple populations,[29-31] with profound changes in case mix. The presentation of heart failure post infarction has also markedly evolved, with an increasing proportion of heart failure cases presenting with preserved ejection fraction.[32] The transformation of the epidemiology of myocardial infarction and of its complications calls for new risk-stratification approaches. Yet, commonly used prognostic tools have not kept pace with the evolution of the disease. In this context, our data suggest that sST2 should be given careful consideration as a novel risk-stratification biomarker. Several important points support this position: firstly, higher values of sST2 are associated with a large increase in the risk of death and heart failure independently of other clinical prognostic indicators; secondly, sST2 is elevated in a large proportion of patients with infarction. The combination of a high prevalence of sST2 elevation at incident myocardial infarction with a large excess risk for adverse outcomes points to the potential for a large benefit in the reduction of adverse outcomes in the event of therapeutic targets to mitigate sST2 elevation.

Some limitations should be acknowledged. As in any observational study, we cannot exclude residual confounding. However, this is likely to be minimal as we used a comprehensive adjustment strategy that controls for known variables commonly used to stratify risk after myocardial infarction and comorbidity. Our study has several important strengths. Our community cohort represents the comprehensive experience of a population, thus, our results are of optimal clinical relevance and are spared the selection biases inherent to clinical trials. Our long follow-up period underscores the prognostic importance of sST2 beyond the acute phase. Finally, our contemporary cohort is relevant to the changing epidemiology of acute myocardial infarction, which is well documented over the last decade.

CONCLUSION

In this community cohort, sST2 is elevated in more than half of patients with incident myocardial infarction. Higher values of sST2 confer a markedly adverse prognosis characterized by a large excess risk of death and heart failure over a long period of follow-up. Measurement of sST2 should be considered as part of contemporary approaches to risk stratification after myocardial infarction.

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