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Serum Soluble ST2

A Potential Novel Mediator in Left Ventricular and Infarct Remodeling After Acute Myocardial Infarction

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Objectives This study sought to assess, for the first time, the relationship between serum concentrations of the soluble interleukin-1 receptor family member ST2 (sST2) and serial change in left ventricular (LV) function after acute myocardial infarction (AMI).

Background Serum sST2 levels are elevated early after AMI and are associated with lower pre-discharge LV ejection fraction and adverse cardiovascular outcomes.

Methods The sST2 levels were measured in 100 patients (mean age 58.9 ± 12.0 years; 77% male), admitted with AMI with resultant LV systolic dysfunction, at baseline and at 12 and 24 weeks. Patients underwent cardiac magnetic resonance imaging and measurement of N-terminal pro-brain natriuretic peptide, norepinephrine, and aldosterone at each time point.

Results Median sST2 decreased from 263.3 pg/ml at baseline to 140.0 pg/ml at 24 weeks ($p < 0.001$). Serum sST2 correlated significantly with LV ejection fraction at baseline ($r = -0.30$, $p = 0.002$) and 24 weeks ($r = -0.23$, $p = 0.026$); change in sST2 correlated with change in LV end-diastolic volume index ($r = -0.24$, $p = 0.023$). Level of sST2 was positively associated with infarct volume index at baseline ($r = 0.26$, $p = 0.005$) and 24 weeks ($r = 0.22$, $p = 0.037$), and with change in infarct volume index ($r = -0.28$, $p = 0.001$). Level of sST2 was significantly higher in patients with greater infarct transmurality and endocardial extent, and in the presence of microvascular obstruction. Level of sST2 correlated significantly with norepinephrine and aldosterone, but not with N-terminal pro-brain natriuretic peptide.

Conclusions Measurement of sST2 early after AMI assists in the prediction of medium-term LV functional recovery. Novel relationships were observed between sST2, infarct magnitude/evolution, and aldosterone. Serum sST2 may be of pathophysiological importance in ventricular and infarct remodeling after AMI. (Effects of Eplerenone on Left Ventricular Remodelling Following Heart Attack; NCT00132093) (J Am Coll Cardiol 2010;55:243–50) © 2010 by the American College of Cardiology Foundation

Risk stratification of patients admitted with acute coronary syndromes is increasingly dependent on measurement of prognostically significant biomarkers. Serum ST2 (interleukin [IL]-1 receptor-like 1, OMIM *601203), a member of the IL-1 receptor family with transmembrane (ST2L) and soluble (sST2) isoforms, may be such a biomarker (1). The transmembrane ST2 isoform is membrane-bound with 3 extracellular immunoglobulin-G domains, a single transmembrane domain, and an intracellular domain homologous to toll-like receptors and other IL-1 receptors (2).

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Soluble ST2 lacks the transmembrane and intracellular domains and is thought to function as a decoy receptor, which neutralizes IL-33, recently demonstrated to be its ligand (3). IL-33 exerts antihypertrophic effects in cultured cardiomyocytes that are antagonized by administration of sST2, and reduces myocardial fibrosis and cardiomyocyte hypertrophy after experimental pressure overload in mice, although interestingly, these effects are not seen in mice lacking the *ST2* gene (4,5). These data suggest a possible

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Abbreviations and Acronyms

AMI = acute myocardial infarction

ceCMR = contrast-enhanced cardiac magnetic resonance

CMR = cardiac magnetic resonance

IL = interleukin

LV = left ventricle/ventricular

LVEDVI = left ventricular end-diastolic volume index

LVEF = left ventricular ejection fraction

LVESVI = left ventricular end-systolic volume index

LVMI = left ventricular mass index

LVSD = left ventricular systolic dysfunction

MBL = Medical and Biological Laboratories

MVO = microvascular obstruction

NT-proBNP = N-terminal pro-brain natriuretic peptide

sST2 = soluble ST2

STEMI = ST-segment elevation myocardial infarction

cardioprotective role for the IL-33/ST2 signaling pathway. In human studies, serum sST2 is elevated early after acute myocardial infarction (AMI) and correlates with creatine kinase and (inversely with) left ventricular ejection fraction (LVEF) (2). Serum sST2 correlates with N-terminal pro-brain natriuretic peptide (NT-proBNP) in patients admitted with ST-segment elevation myocardial infarction (STEMI) and predicts subsequent 30-day mortality and heart failure (6,7). Additionally, serum sST2 is elevated and is of predictive value in acutely dyspneic patients with and without decompensated acute heart failure, and in chronic heart failure (5,8,9).

That sST2 predicts adverse cardiovascular outcome, and is related to LVEF after AMI, suggests that it may have a role in adverse left ventricular (LV) remodeling, but this has yet to be evaluated. We, therefore, examined the relationships between serum sST2, parameters of LV function, and a variety of circulating mediators in a cohort of patients admitted with AMI.

Methods

Patients. The subjects of this study were participants in a randomized, double-blinded, placebo-controlled clinical trial investigating the effects of eplerenone on LV remodeling after AMI in patients with left ventricular systolic dysfunction (LVSD) (10). Inclusion criteria were as follows: ≥18 years of age; able to provide written, informed consent; admitted with AMI in the 1 to 14 days before enrollment; and LVEF <40% on screening transthoracic echocardiography—Simpson's biplane rule. Exclusion criteria were clinical or radiological heart failure (Killip score >1); established diabetes mellitus; pregnancy; serum creatinine >220 μmol/l; serum potassium >5 mmol/l; and conventional contraindications to cardiac magnetic resonance (CMR). The study complies with the Declaration of Helsinki, and was approved by the local ethics committee.

Procedures. Eligible patients had venous blood collected (after 20 min of supine rest) for measurement of blood chemistry, sST2, NT-proBNP, norepinephrine, and aldosterone, after which contrast-enhanced cardiac magnetic resonance (ceCMR) imaging was performed. Patients were then randomly assigned to double-blind eplerenone or placebo, with repeat ceCMR and biomarker sampling at 12 and 24 weeks.

Measurement of circulating biomarkers. Blood was collected in chilled tubes containing potassium ethylenediamine tetra-acetic acid (1 mg/ml blood) and aprotinin (50 KIU/ml blood) for NT-proBNP, lithium heparin (20 U/ml) tubes for norepinephrine and aldosterone, and in plain tubes (and allowed to clot) for sST2, at room temperature. Samples were then centrifuged at 3,000 rpm for 15 min at ambient temperature, and the supernatant immediately frozen and stored at −70°C until later blinded batched analysis. The NT-proBNP, norepinephrine, and aldosterone samples were subjected to 1, and sST2 samples to 2, freeze-thaw cycles. The NT-proBNP was measured using a chemiluminescent assay kit (Roche Diagnostics, West Sussex, United Kingdom) on an Elecsys 2010 autoanalyzer (coefficient of variation <2%, limit of detection of 5 pg/ml). Plasma norepinephrine was assayed by high-performance liquid chromatography and electrochemical detection (within and between assay coefficient of variation both <10%; normal range in healthy volunteers <4 nmol/l). Plasma aldosterone concentration was measured using a solid phase (coated tube) radioimmunoassay kit (Diagnostic Products Corporation UK Ltd., Gwynedd, United Kingdom). Intrabatch and interbatch precision was <10% over the sample concentration range. Serum sST2 was quantified using a human IL-1 R4/ST2 enzyme-linked immunosorbent assay (R&D Systems, Abingdon, United Kingdom), with coefficient of variation <5% and a lower limit of detection of 32 pg/ml.

ceCMR protocol. ceCMR was performed using a 1.5-T Siemens (Erlangen, Germany) Sonata with a phased-array chest coil, during breath-hold, and gated to the electrocardiogram. A steady-state free-precession sequence was used to acquire a short-axis cine stack of the LV from base to apex of 8-mm thick slices with a 2-mm interslice gap. Gadolinium diethylenetriaminepenta-acetate (GE Healthcare, Waukesha, Wisconsin) was then administered (0.1 mmol/kg) as a rapid intravenous bolus. After a 15-min delay, a contrast-sensitive segmented inversion recovery sequence was used to acquire a second stack of short-axis images (positions copied from the cine stack), of thickness 8 mm, with interslice gap 2 mm; the time to inversion was varied within the range 200 to 300 ms to obtain optimal nulling of the myocardium for the delayed enhancement sequences.

CONTRAST-ENHANCED CMR ANALYSIS. Post-processing was performed using Argus software (Siemens, Erlangen, Germany). Manual planimetry, performed by 1 observer blinded to treatment allocation, was used to trace the epicardial and endocardial contours of each short-axis slice acquired in the cine-stack, allowing calculation of LV volumes, LVEF, and LV mass. Infarcted LV myocardium on ceCMR was defined as regional delayed hyperenhancement after gadolinium injection involving at least the subendocardium. Using standardized contrast settings, the infarcted volume of LV myocardium, defined as any region of signal intensity higher than normal (remote) myocardium, was delineated manually by 1 observer blinded to

treatment allocation. In addition, on the initial (acute) ceCMR scan only, the anatomical location, transmurality, and endocardial extent of the infarct were recorded, as was the presence or absence of late microvascular obstruction (MVO).

The anatomical location of the infarct was based on the American Heart Association standardized 17-segment model (11). Infarct location was categorized as anterior, lateral, or inferior, defined as the location containing the highest percentage of infarcted myocardium. If the infarct encompassed equivalent anterior and lateral or inferior and lateral segments, the site was classified as anterolateral or inferolateral, respectively. Infarct transmurality score was calculated by visually deciding the transmural extent per segment in quarters (1 = 1% to 25%, 2 = 26% to 50%, 3 = 51% to 75%, 4 = 76% to 100%) and calculating the mean (12). Endocardial extent of the infarct was defined as the mean of the circumferential extent of the infarct at each of the 3 short-axis slices used in the American Heart Association model (11). Late MVO was defined as late hypoenhancement within a hyperenhanced region on the delayed ceCMR images that persisted for ≥10 min after contrast injection (13).

Statistics. The ceCMR measurements were adjusted for total body surface area, creating the following indexed quantities: left ventricular end-systolic volume index (LVESVI), left ventricular end-diastolic volume index (LVEDVI), left ventricular mass index (LVMI), and LV infarct volume index. Only patients with both a baseline and 24-week follow-up scan were analyzed; patients with an incomplete dataset were excluded. Left ventricular remodeling was defined as an increase over time of 10 ml/m^2 in LVESVI and/or LVEDVI, as described previously (14,15). All baseline biomarker measurements were taken before randomization, and serial biomarker data were initially analyzed regardless of parent study treatment allocation, then by treatment group. Normally distributed continuous data are expressed as mean values (±SD). Non-normally distributed continuous data are expressed as median (interquartile range). Differences between mean values were analyzed using the Student *t* test, and those between median values by the Mann-Whitney *U* test. Paired comparisons in biomarker concentrations over time were performed using the Wilcoxon matched-pairs signed-rank test.

Non-normal data were logarithmic-transformed before correlative analysis; Pearson's and Spearman's correlation coefficients were used for parametric and nonparametric variables, respectively. All statistical analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, Illinois). A probability value of $p < 0.05$ was considered significant.

Results

Baseline characteristics are shown in Table 1. The mean time from AMI to screening transthoracic echocardiography was 34 h, and mean time to the first ceCMR scan was 97 h; biomarker sampling was performed at a mean 46 h after AMI. Paired analysis of both ceCMR and biomarker results was performed in the 93 patients who completed the entire 24-week follow-up (3 died, 4 withdrew).

Table 1 Baseline Characteristics of Patients

	AMI Cohort (n = 100)
Patient demographics	
Age, yrs	58.9 (12.0)
Male	77
Medical history	
Previous MI	7.0
Previous CABG	5.0
Previous PCI	2.0
Angina	37.0
Current smoker	55.0
Hypertension	35.0
Hypercholesterolemia*	25.0
Asthma/COPD	4.0
Infarct type/site	
STEMI	90.0†
Non-STEMI	10.0‡
Infarct characteristics	
Infarct volume index, ml/m^2	34.0 (21.2)
Endocardial extent	36.8 (11.5)
Transmurality score	3.3 (0.6)
Late microvascular obstruction	56.0
Treatment	
Thrombolysis	54.0
Primary PCI	27.0
Rescue PCI	26.0
Angiography performed	85.0
PCI performed	74.0
Biochemistry	
Serum creatinine, mg/dl	1.13 (0.24)
Serum sST2, pg/ml, median (IQR)	263.3 (139.4–491.5)
NT-proBNP, pg/ml, median (IQR)	1,883 (997–3,181)
Norepinephrine, mmol/l, median (IQR)	2.90 (1.90–3.78)
Aldosterone, pmol/l, median (IQR)	131.0 (69.0–290.0)
Discharge medication	
Aspirin	96.0
Clopidogrel	82.0
Beta-blocker	93.0
ACE inhibitor or ARB	94.0
Statin	98.0
Furosemide	21.0
Eplerenone	50.0

Unless otherwise stated, continuous data are expressed as mean (SD), and categorical data are expressed as percentages of the relevant treatment group. *Serum cholesterol >5 mmol/l and/or receiving lipid-lowering therapy before admission. †47 anterior ± lateral, 39 inferior ± lateral, 4 lateral. ‡8 anterior ± lateral, 2 inferior ± lateral.

ACE = angiotensin-converting enzyme; AMI = acute myocardial infarction; ARB = angiotensin-receptor blocker; CABG = coronary artery bypass graft surgery; COPD = chronic obstructive pulmonary disease; IQR = interquartile range; MI = myocardial infarction; NT-proBNP = N-terminal pro-brain natriuretic peptide; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

Changes in biomarker concentrations after AMI. Serum sST2 concentration, expressed as median (interquartile range [IQR]), decreased significantly (from 263.3 pg/ml [IQR 139.4

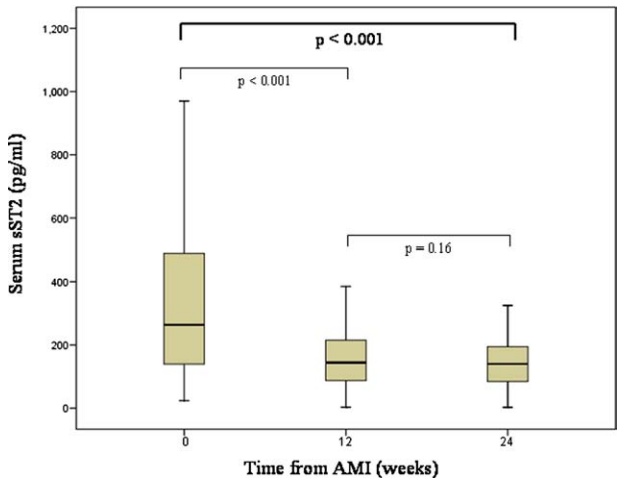

Figure 1 Serial Change in Median sST2 Over Time After AMI

Serial changes in median serum soluble ST2 (sST2) over time after acute myocardial infarction (AMI) are shown. **Boxes** represent interquartile ranges.

to 491.5 pg/ml] at baseline to 140.0 pg/ml [IQR 83.0 to 196.2 pg/ml] at 24 weeks; $p < 0.001$). This decrease occurred predominantly between baseline and 12 weeks (Fig. 1).

Over the 24 weeks of follow-up, plasma NT-proBNP concentration decreased significantly (from 1,883 pg/ml [IQR 997 to 3,181 pg/ml] to 335 pg/ml [IQR 177 to 728 pg/ml]; $p < 0.001$), as did norepinephrine (2.90 mmol/l [IQR 1.90 to 3.80 mmol/l] vs. 2.50 mmol/l [IQR 1.80 to 3.50 mmol/l]; $p = 0.013$); plasma aldosterone did not vary significantly (131 pmol/l [IQR 69 to 290 pmol/l] at baseline vs. 153 pmol/l [IQR 86 to 287 pmol/l] at 24 weeks; $p = 0.33$).

Serum sST2 concentration and LV function after AMI. Serum sST2 concentrations were non-normally distributed and, accordingly, were logarithmic-transformed before analysis. The change over time in each measured ceCMR parameter is shown in Table 2. Baseline sST2 correlated inversely with baseline LVEF ($r = -0.30$, $p = 0.002$) and baseline infarct volume index ($r = 0.26$, $p = 0.005$) but not with baseline LVESVI, LVEDVI, or LVMI (Table 3). Baseline sST2 correlated significantly with 24-week LVEF ($r = -0.23$, $p = 0.026$) and infarct volume index ($r = 0.22$, $p = 0.037$) but not with 24-week LV volumes or LVMI. Baseline sST2 correlated inversely with change in (Δ) infarct volume index ($r = -0.28$, $p = 0.009$) but not with change in any other ceCMR parameter.

Change in sST2 from baseline to 24 weeks correlated significantly with ΔLVEDVI ($r = -0.24$, $p = 0.023$) and with change in infarct volume index ($r = 0.21$, $p = 0.043$) but not with ΔLVESVI, ΔLVEF, or ΔLVMI (Table 3).

Comparison of baseline sST2 concentration in patients with ΔLVESVI >10 ml/m^2 ($n = 16$) and patients with ΔLVESVI ≤10 ml/m^2 ($n = 77$) revealed a trend toward a higher sST2 in the former group, namely, patients in whom remodeling occurred (379.6 pg/ml [IQR 201.4 to 615.5 pg/ml] vs. 181.4 pg/ml [IQR 118.1 to 228.8 pg/ml], respectively; $p = 0.054$). Baseline sST2 was significantly higher in patients ($n = 29$) with ΔLVEDVI >10 ml/m^2 than in patients ($n = 64$) with ΔLVEDVI ≤10 ml/m^2 (358.0 pg/ml [IQR 259.7 to 647.1 pg/ml] vs. 197.5 pg/ml [IQR 129.2 to 393.6 pg/ml]; $p = 0.041$).

Serum sST2 concentration and infarct characteristics. Baseline infarct characteristics are shown in Table 1. There were no significant differences in serum sST2 between anterior/anterolateral ($n = 55$; 278.6 pg/ml [IQR 151.4 to 493.6 pg/ml]), inferior/inferolateral ($n = 41$; 261.2 pg/ml [IQR 127.2 to 569.5 pg/ml]), and lateral ($n = 4$; 181.8 pg/ml [IQR 116.4 to 181.8 pg/ml]) sites of infarction (Fig. 2A). Serum sST2 correlated significantly with the endocardial extent of the infarct ($r = 0.26$, $p = 0.008$). The presence of late MVO was associated with a significantly higher serum sST2 (347.6 pg/ml [IQR 192.3 to 631.0 pg/ml] vs. 185.7 pg/ml [IQR 126.5 to 330.3 pg/ml] without MVO; $p = 0.001$) (Fig. 2B). Serum sST2 was significantly higher in patients with a transmurality score at or above the median compared with patients whose score was below the median (289.3 pg/ml [IQR 183.0 to 580.1 pg/ml] vs. 203.8 pg/ml [IQR 126.3 to 335.5 pg/ml]; $p = 0.031$) (Fig. 2C).

Serum sST2 and biochemical correlates after AMI. The relationships between baseline NT-proBNP, norepinephrine, and aldosterone and ceCMR parameters are shown in Table 3. Baseline sST2 correlated significantly with baseline norepinephrine ($r = 0.21$, $p = 0.034$) and aldosterone ($r = 0.28$, $p = 0.006$) but not with NT-proBNP ($r = 0.14$, $p = 0.15$). Baseline sST2 also correlated with Δnorepinephrine ($r = -0.25$, $p = 0.014$) but not with Δaldosterone or ΔNT-proBNP.

Change in sST2 correlated significantly with Δaldosterone ($r = 0.26$, $p = 0.012$) and Δnorepinephrine ($r = 0.23$, $p = 0.024$) but not with ΔNT-proBNP ($r = 0.15$, $p = 0.14$).

Treatment effect of eplerenone. Eplerenone had no significant effect on serum sST2 concentration over time. Baseline serum sST2 concentration was similar within both randomization groups (272.4 pg/ml [IQR 151.1 to 528.6 pg/ml] in the placebo group vs. 259.1 pg/ml [IQR 129.7 to 410.1 pg/ml] in the eplerenone group; $p = 0.78$). Over 24 weeks, the change in serum sST2 concentration was −66.4

Table 2 Serial ceCMR Parameters of Left Ventricular Function for Entire Study Cohort (n = 100)

ceCMR Parameter	Baseline	12 Weeks	24 Weeks	p Value*
LVESVI, ml/m^2	43.6 (15.2)	43.3 (20.9)	43.1 (20.7)	0.77
LVEDVI, ml/m^2	83.9 (18.0)	89.4 (25.6)	88.1 (23.0)	0.011
LVEF, %	48.7 (8.8)	53.4 (10.4)	53.0 (12.0)	<0.001
LVMI, g/m^2	74.4 (15.3)	67.6 (15.8)	67.1 (14.3)	<0.001
Infarct volume index, ml/m^2	34.0 (21.2)	22.2 (14.4)	20.9 (12.9)	<0.001

All values presented as mean (SD). *Comparison between baseline value and 24-week value.
ceCMR = contrast-enhanced cardiac magnetic resonance; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index; LVMI = left ventricular mass index.

Table 3 Spearman Correlation Coefficients for Circulating Biomarkers, Sampled at Baseline, and ceCMR Parameters of LV Remodeling

	Baseline			
	log_{10} (Serum sST2)	log_{10} (NT-proBNP)	log_{10} (Norepinephrine)	log_{10} (Aldosterone)
Baseline				
LVESVI	0.17	0.33†	0.17	0.25*
LVEDVI	0.01	0.19	0.10	0.15
LVEF	−0.30†	−0.39†	−0.22*	−0.31†
LVMI	0.05	0.05	0.23*	0.22*
Infarct volume	0.26†	0.26†	0.17	0.39†
24 weeks				
LVESVI	0.17	0.43†	0.23*	0.34†
LVEDVI	0.06	0.30†	0.09	0.18
LVEF	−0.23†	−0.45†	−0.31†	−0.41†
LVMI	0.03	0.02	0.16	0.22*
Infarct volume	0.22*	0.33†	0.17	0.41†

	ΔsST2‡		ΔNT-proBNP‡		ΔNorepinephrine‡		ΔAldosterone‡	
ΔceCMR parameter (0 to 24 weeks)								
ΔLVESVI, ml/m^2	0.11	−0.13	0.26†	−0.14	0.10	0.08	0.28†	−0.23*
ΔLVEDVI, ml/m^2	0.18	−0.24*	0.19	−0.06	0.01	−0.02	0.2	−0.33†
ΔLVEF, %	−0.01	0.01	−0.19	0.08	−0.15	−0.12	−0.21*	0.07
ΔLVMI, g/m^2	0.03	−0.01	−0.06	0.12	−0.19	0.07	−0.07	−0.07
ΔInfarct volume, ml/m^2	−0.28†	0.21*	−0.08	0.10	−0.14	0.15	−0.34†	0.19

*$p < 0.05$. †$p < 0.01$. ‡Change in each biomarker between baseline and 24 weeks.
sST2 = soluble ST2; other abbreviations as in Tables 1 and 2.

pg/ml (IQR −226.2 to −10.1 pg/ml) in the placebo group and −130.7 pg/ml (IQR −409.3 to −228.0 pg/ml) in the eplerenone group ($p = 0.13$).

To determine whether an interaction exists between eplerenone therapy and sST2, we divided patients into 4 groups according to baseline sST2 concentration and placebo/eplerenone therapy—sST2 less than median, placebo therapy ("low sST2/plac"); sST2 less than median, eplerenone therapy ("low sST2/epl"); sST2 median or greater, placebo therapy ("high sST2/plac"); and sST2 median or greater, eplerenone therapy ("high sST2/epl")—and compared remodeling outcomes (Table 4). There were relatively small changes in LVESVI and LVEDVI in the low sST2 groups, and adverse remodeling (i.e., increases in ventricular volumes) only occurred in the high sST2 patients treated with placebo. These increases appeared to be attenuated in high sST2 patients treated with eplerenone.

Eplerenone treatment was associated with a significant increase in aldosterone over time (Δaldosterone −10.1 pmol/l [IQR −135.0 to 85.0 pmol/l] in placebo group vs. +41.0 pmol/l [IQR −29.5 to 217.0 pmol/l] in eplerenone group; $p = 0.038$) but had no significant effect on NT-proBNP or norepinephrine compared with placebo. In the parent study, eplerenone had a modest antiremodeling effect, but only after covariate adjustment (10).

Discussion

In our cohort of patients, all of whom were required to have depressed LVEF, we have not only confirmed that there is a relationship between sST2 and LV function early after AMI, but have also shown for the first time that sST2 is associated with medium-term LV function, and additionally, that sST2 is related to infarct magnitude and infarct remodeling over time. We report novel data on potential relationships between sST2, aldosterone, and norepinephrine after AMI. We also provide some evidence to support the possibility that eplerenone may attenuate LV remodeling in patients with higher sST2 concentrations (although this analysis is limited by small numbers).

Both sST2 isoforms—ST2L and sST2—are transcriptionally induced by the application of biomechanical strain to rodent cardiomyocytes and cardiac fibroblasts in vitro (2,4). Not only is sST2 elevated in vivo after experimental AMI in mice, but it has also been shown to be elevated in the serum of human subjects after AMI, in acute heart failure, and in chronic heart failure (2,4–9). When measured early after AMI, significant associations have been found between sST2, higher creatine kinase concentrations, and lower pre-discharge LVEF (2,7). Moreover, baseline sST2 predicts 30-day occurrence of heart failure or death after STEMI and, when combined with NT-proBNP, significantly improves risk stratification in this condition (6,7). sST2 is also of prognostic benefit for both acute heart failure and chronic heart failure, in which it is associated with poorer LV function and higher New York Heart Association functional class (5,8,9). The relationship between sST2 and serial change in LV function after AMI has not previously been characterized. Using a gold standard technology for LV functional assessment, ceCMR, which additionally affords detailed infarct examination, we report

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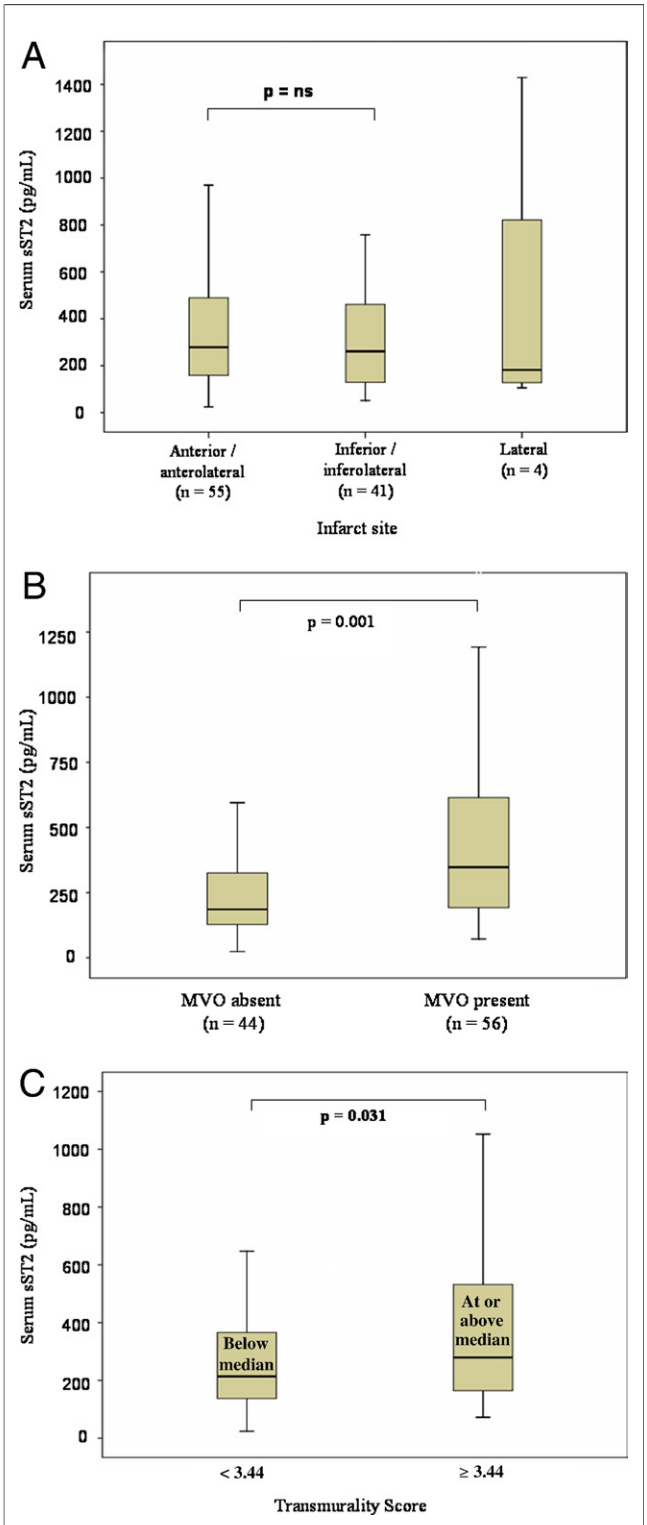

Figure 2 **Serum sST2 and Infarct Characteristics After AMI**

Comparison of serum soluble ST2 (sST2) concentrations after acute myocardial infarction (AMI) according to **(A)** contrast-enhanced cardiac magnetic resonance-measured anatomical infarct site (note: lateral infarct site not used in comparative analysis with other infarct sites, as n = 4), **(B)** presence of late microvascular obstruction (MVO), and **(C)** median transmurality score (3.44). **Boxes** represent interquartile ranges.

for the first time on the relationship between sST2, LV remodeling, and infarct characteristics after AMI.

In our study patients, who were all required to have LVSD after AMI, we found a significant correlation between sST2 (measured in the first few days after AMI) and pre-discharge LVEF, in keeping with recent clinical studies. In the largest published study examining sST2 in AMI, a correlation (albeit weak) was found between sST2 and lower LVEF early after STEMI in 551 patients enrolled in the CLARITY–TIMI 28 (Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis In Myocardial Infarction 28) trial (7). A similar relationship was seen in 69 predominantly STEMI patients enrolled in the HEART (Healing and Early Afterload Reducing Therapy) study (2). Our findings, that baseline sST2 correlates with medium-term (24-week) LVEF and that greater adverse LV remodeling was seen in patients with the highest baseline sST2, are novel. Whether sST2 has a pathophysiological role in post-infarction remodeling or whether it simply identifies a population with poorer LV function who would be more likely to remodel, is unclear; data from infarct characteristics and biomarker analysis provide further insights.

We assessed the relationship between sST2, baseline infarct characteristics, and infarct evolution over time. Although we did not find any relationship with infarct location, we have shown that sST2, measured early after AMI, was associated with greater baseline infarct volume, correlated with the endocardial extent of infarction, and was higher in patients with greater infarct transmurality, all parameters of large infarction. We also found that sST2 was higher in patients displaying MVO, which is known to be associated with greater baseline LV volumes, more significant remodeling, and adverse cardiovascular outcome after AMI (16,17). Over time, we found a correlation between sST2 and 24-week infarct volume, and an inverse relationship with Δ infarct volume, which occurs as peri-infarct edema resolves and the infarcted myocardium remodels (18). These data suggest an association between infarct magnitude and serum sST2 release.

We observed a novel correlation between sST2 and plasma aldosterone. Aldosterone has strong profibrotic effects on the heart—both reparative fibrosis in the infarct zone and reactive fibrosis in noninfarct myocardium—some of which are thought to be mediated by mineralocorticoid receptor activation on cardiac fibroblasts (19,20). Aldosterone antagonism can attenuate or even reverse myocardial fibrosis, with concomitant improvement in LV function (21,22). Significant improvements in cardiovascular outcomes have been demonstrated using aldosterone antagonists in survivors of AMI with resultant LVSD and heart failure (or diabetes mellitus) and in advanced chronic heart failure (23,24). We observed statistically significant associations between plasma aldosterone and parameters of LV remodeling in our cohort.

Comparison of baseline sST2 concentrations in our study with published studies in patients with AMI and heart

Table 4 Comparison of Remodeling Outcomes According to Baseline sST2 Concentration and Placebo Versus Eplerenone Therapy

		Baseline Values			Change Over Time	
Group	n	Median sST2 (IQR)	LVESVI	LVEDVI	ΔLVESVI	ΔLVEDVI
Low/plac	22	150.8 (58.6–261.2)	50.3 (18.8)*	93.2 (22.4)†	−4.0 (16.8)	0.8 (16.6)‡
Low/epl	26	132.8 (51.9–384.9)	35.2 (9.3)*	77.5 (12.6)†	−0.4 (9.8)	2.8 (9.6)‡
High/plac	23	544.7 (265.4–1,876.4)	48.7 (16.7)*	86.6 (19.9)	4.2 (15.29)	12.1 (17.3)‡
High/epl	22	423.8 (266.6–1,522.1)	42.4 (10.0)	81.2 (12.8)	−1.7 (13.9)	1.2 (17.5)‡

Using univariate analysis of variance: *LVESVI significantly lower in "low/epl" group than in "low/plac" and "high/plac" groups at baseline ($p = 0.001$); †LVEDVI significantly lower in "low/epl" group than in "low/plac" group ($p = 0.01$); ‡ΔLVEDVI significantly higher in "high/plac" group than in the other 3 groups ($p = 0.050$).

Δ = change between baseline and 24 weeks; low/epl = baseline sST2 less median, randomized to eplerenone; low/plac = baseline sST2 less than median, randomized to placebo; high/epl = baseline sST2 median or greater, randomized to eplerenone; high/plac = baseline sST2 median or greater, randomized to placebo; other abbreviations as in Tables 1 to 3.

failure is rendered difficult by not only variations in timing of sST2 sampling but also by the analysis kits used, with most studies to date using a Medical and Biological Laboratories (MBL) assay (5–7,9,25). The R&D Systems assay used in this study has not been harmonized to the MBL assay; thus, the exact numerical values generated may not be interchangeable. It does appear, however, that the magnitude of sST2 elevation (in pg/ml using the R&D assay) in this study is comparable to the sST2 concentrations (in ng/ml) measured using the MBL assay in such related studies, although direct numerical comparison is perhaps misleading.

Study limitations. The parent study was powered for CMR end points, hence the relatively small sample size (n = 100) (10). Where relevant, we have acknowledged findings from more appropriately powered studies examining sST2 in AMI. The study was neither designed nor powered for analysis of effects of sST2 on remodeling or its interaction with biomarkers; therefore, these results should be treated as hypothesis-generating only. Our results pertain only to patients with LVSD after AMI, and cannot be generalized to all post-MI patients. We sampled serum sST2 only once in the early post-infarction phase, at a mean 46 h after AMI. The precise temporal profile of serum sST2 concentration after AMI in humans has yet to be characterized, but data from the CLARITY–TIMI 28 trial show a small but significant decrease in sST2 between admission with STEMI and angiography 96 h later (7). We cannot assume that we measured "peak" sST2 after AMI, merely a "pre-discharge" serum concentration. We did not simultaneously measure IL-33 and therefore cannot comment on the IL-33/sST2 ratio, but this is a clear focus for future research in both AMI and heart failure. Serum sST2 concentrations are elevated in noncardiac conditions including asthma, trauma, sepsis, malignancy, and autoimmune disease; although we did not adjust for these conditions, they are only applicable to a very small number of our trial cohort and would thus be unlikely to influence our results (26). The significant correlations between sST2, LV functional parameters, and neurohormones reported in this study are modest and must therefore be interpreted with caution, but it is noteworthy that our correlation coefficients are similar in magnitude, if not higher, than those in published studies of sST2 in patients with AMI and heart failure (2,8,9). Finally, it must be appreciated that correlations between measured quantities, as reported within this study, do not imply definite biologic interaction.

Conclusions

We have shown that measurement of sST2 early after AMI assists in the prediction of medium-term LV functional recovery after AMI, and that direct relationships exist between sST2, infarct magnitude, and infarct remodeling. Eplerenone, which had a modest antiremodeling effect in the parent study, may attenuate remodeling to a greater extent in patients with a higher baseline sST2 (10). We also, for the first time, report on a relationship between sST2 and circulating aldosterone, and suggest that the IL-33/sST2 signaling system and the RAAS may be interlinked, raising the possibility of a direct role for the IL-33/sST2 system in the pathogenesis of post-infarction remodeling, which merits further study as the role of this novel biomarker is further unraveled.

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REFERENCES

1. Tominaga S, Kuroiwa K, Tago K, Iwahana H, Yanagisawa K, Komatsu N. Presence and expression of a novel variant form of ST2 gene product in human leukemic cell line UT-7/GM. Biochem Biophys Res Commun 1999;264:14–8.
2. Weinberg EO, Shimpo M, De Keulenaer GW, et al. Expression and regulation of ST2, an interleukin-1 receptor family member, in cardiomyocytes and myocardial infarction. Circulation 2002;106:2961–6.
3. Schmitz J, Owyang A, Oldham E, et al. IL-33, an interleukin-1-like cytokine that signals via the IL-1 receptor-related protein ST2 and induces T helper type 2-associated cytokines. Immunity 2005;23:479–90.
4. Sanada S, Hakuno D, Higgins LJ, Schreiter ER, McKenzie AN, Lee RT. IL-33 and ST2 comprise a critical biomechanically induced and cardioprotective signaling system. J Clin Invest 2007;117:1538–49.
5. Januzzi JL Jr., Peacock WF, Maisel AS, et al. Measurement of the interleukin family member ST2 in patients with acute dyspnea: results from the Pro-Brain Natriuretic Peptide Investigation of Dyspnea in the Emergency Department study. J Am Coll Cardiol 2007;50:607–13.
6. Shimpo M, Morrow DA, Weinberg EO, et al. Serum levels of the interleukin-1 receptor family member ST2 predict mortality and

clinical outcome in acute myocardial infarction. Circulation 2004;109: 2186–90.
7. Sabatine MS, Morrow DA, Higgins LJ, et al. Complementary roles for biomarkers of biomechanical strain ST2 and N-terminal prohormone B-type natriuretic peptide in patients with ST-elevation myocardial infarction. Circulation 2008;117:1936–44.
8. Weinberg EO, Shimpo M, Hurwitz S, Tominaga S, Rouleau JL, Lee RT. Identification of serum soluble ST2 receptor as a novel heart failure biomarker. Circulation 2003;107:721–6.
9. Rehman SU, Mueller T, Januzzi JL Jr. Characteristics of the novel interleukin family biomarker ST2 in patients with acute heart failure. J Am Coll Cardiol 2008;52:1458–65.
10. Weir RA, Mark PB, Petrie CJ, et al. Left ventricular remodeling after acute myocardial infarction: does eplerenone have an effect? Am Heart J 2009;157:1088–96.
11. Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. Circulation 2002;105:539–42.
12. Kim RJ, Wu E, Rafael A, et al. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. N Engl J Med 2000;343:1445–53.
13. Lund GK, Stork A, Saeed M, et al. Acute myocardial infarction: evaluation with first-pass enhancement and delayed enhancement MR imaging compared with 201Tl SPECT imaging. Radiology 2004;232: 49–57.
14. Zhang Y, Yip GW, Chan AK, et al. Left ventricular systolic dyssynchrony is a predictor of cardiac remodeling after myocardial infarction. Am Heart J 2008;156:1124–32.
15. Bellenger NG, Davies LC, Francis JM, Coats AJ, Pennell DJ. Reduction in sample size for studies of remodeling in heart failure by the use of cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2000;2:271–8.
16. Wu KC, Zerhouni EA, Judd RM, et al. Prognostic significance of microvascular obstruction by magnetic resonance imaging in patients with acute myocardial infarction. Circulation 1998;97:765–72.
17. Ito H, Maruyama A, Iwakura K, et al. Clinical implications of the "no reflow" phenomenon. A predictor of complications and left ventricular remodeling in reperfused anterior wall myocardial infarction. Circulation 1996;93:223–8.
18. Schroeder AP, Houlind K, Pedersen EM, Nielsen TT, Egeblad H. Serial magnetic resonance imaging of global and regional left ventricular remodeling during 1 year after acute myocardial infarction. Cardiology 2001;96:106–14.
19. Brilla CG, Matsubara LS, Weber KT. Anti-aldosterone treatment and the prevention of myocardial fibrosis in primary and secondary hyperaldosteronism. J Mol Cell Cardiol 1993;25:563–75.
20. Weber KT. Aldosterone in congestive heart failure. N Engl J Med 2001;345:1689–97.
21. Delyani JA, Robinson EL, Rudolph AE. Effect of a selective aldosterone receptor antagonist in myocardial infarction. Am J Physiol Heart Circ Physiol 2001;281:H647–54.
22. Fraccarollo D, Galuppo P, Hildemann S, Christ M, Ertl G, Bauersachs J. Additive improvement of left ventricular remodeling and neurohormonal activation by aldosterone receptor blockade with eplerenone and ACE inhibition in rats with myocardial infarction. J Am Coll Cardiol 2003;42:1666–73.
23. Pitt B, Zannad F, Remme WJ, et al. The effects of spironolactone on morbidity and mortality in patients with severe heart failure. Randomised Aldactone Evaluation Study Investigators. N Engl J Med 1999; 4341:709–17.
24. Pitt B, Remme WJ, Zannad F, et al., for the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 2003;348:1309–21.
25. Boisot S, Beede J, Isakson S, et al. Serial sampling of ST2 predicts 90-day mortality following destabilized heart failure. J Card Fail 2008;14:732–8.
26. Kakkar R, Lee RT. The IL-33/ST2 pathway: therapeutic target and novel biomarker. Nat Rev Drug Discov 2008;7:827–40.

Key Words: ST2 ■ cardiac magnetic resonance ■ myocardial infarction ■ remodeling ■ aldosterone.