

Role of Soluble ST2 Levels and Beta-Blockers Dosage on Cardiovascular Events of Patients with Unselected ST-Segment Elevation Myocardial Infarction

Wei-Ping Huang, Xuan Zheng, Lei He, Xi Su, Cheng-Wei Liu, Ming-Xiang Wu
Department of Cardiology, Wuhan Asia Heart Hospital, Wuhan, Hubei 430022, China

Abstract

Background: Serum soluble ST2 (sST2) levels are elevated early after acute myocardial infarction and are related to adverse left ventricular (LV) remodeling and cardiovascular outcomes in ST-segment elevation myocardial infarction (STEMI). Beta-blockers (BB) have been shown to improve LV remodeling and survival. However, the relationship between sST2, final therapeutic BB dose, and cardiovascular outcomes in STEMI patients remains unknown.

Methods: A total of 186 STEMI patients were enrolled at the Wuhan Asia Heart Hospital between January 2015 and June 2015. All patients received standard treatment and were followed up for 1 year. Serum sST2 was measured at baseline. Patients were divided into four groups according to their baseline sST2 values (high >56 ng/ml vs. low ≤56 ng/ml) and final therapeutic BB dose (high ≥47.5 mg/d vs. low <47.5 mg/d). Cox regression analyses were performed to determine whether sST2 and BB were independent risk factors for cardiovascular events in STEMI.

Results: Baseline sST2 levels were positively correlated with heart rate ($r = 0.327$, $P = 0.002$), Killip class ($r = 0.408$, $P = 0.000$), Ig N-terminal prohormone B-type natriuretic peptide ($r = 0.467$, $P = 0.000$), Ig troponin I ($r = 0.331$, $P = 0.000$), and Ig C-reactive protein ($r = 0.307$, $P = 0.000$) and negatively correlated to systolic blood pressure ($r = -0.243$, $P = 0.009$) and LV ejection fraction ($r = -0.402$, $P = 0.000$). Patients with higher baseline sST2 concentrations who were not titrated to high-dose BB therapy ($P < 0.0001$) had worse outcomes. Baseline high sST2 (hazard ratio [HR]: 2.653; 95% confidence interval [CI]: 1.201–8.929; $P = 0.041$) and final low BB dosage (HR: 1.904; 95% CI, 1.084–3.053; $P = 0.035$) were independent predictors of cardiovascular events in STEMI.

Conclusions: High baseline sST2 levels and final low BB dosage predicted cardiovascular events in STEMI. Hence, sST2 may be a useful biomarker in cardiac pathophysiology.

Key words: Adrenergic Beta-Antagonists; Prognosis; ST-Elevation Myocardial Infarction; ST2

INTRODUCTION

The *ST2* gene (also known as T1 or interleukin [IL]-1 receptor-like-1) is a member of the IL-1 receptor family. The products of this gene include transmembrane (ST2L) and soluble ST2 (sST2) isoforms.^[1] A genomic study showed that *ST2* gene was strongly induced by mechanical strain on cardiac fibroblasts and cardiomyocytes.^[2] Concentrations of sST2 increased under myocardial overload due to myocardial infarction (MI) and were found to be related to adverse left ventricular (LV) remodeling and cardiovascular outcomes.^[3] Shimpo *et al.*^[4] revealed a predictive value of sST2 in patients with ST-segment elevation MI (STEMI) since baseline levels

of sST2 were significantly higher in patients who died or developed new congestive heart failure (HF) during 30-day follow-up. However, the exact mechanism of sST2 in infarct magnitude and remodeling remains unclear.

Address for correspondence: Dr. Lei He,
Department of Cardiology, Wuhan Asia Heart Hospital, Wuhan,
Hubei 430022, China
E-Mail: helei0528@126.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

© 2018 Chinese Medical Journal | Produced by Wolters Kluwer - Medknow

Received: 11-12-2017 **Edited by:** Yuan-Yuan Ji

How to cite this article: Huang WP, Zheng X, He L, Su X, Liu CW, Wu MX. Role of Soluble ST2 Levels and Beta-Blockers Dosage on Cardiovascular Events of Patients with Unselected ST-Segment Elevation Myocardial Infarction. *Chin Med J* 2018;131:1282-8.

Access this article online

Quick Response Code:



Website:
www.cmj.org

DOI:
10.4103/0366-6999.232819

A study in patients with acute MI (AMI) with resultant LV systolic dysfunction revealed that patients with elevated sST2 may benefit from mitigating LV remodeling therapies.^[5] Beta-blockers (BBs) have been shown to improve LV remodeling and were suggested to titrate to target doses (190 mg) as tolerated in STEMI.^[6] Gaggin *et al.*^[7] revealed that sST2 measurement identified patients with chronic HF who may benefit from higher BB doses. However, the relationship between sST2, BB therapy, and cardiovascular outcomes in STEMI patients remains unknown.

METHODS

Ethical approval

The study was conducted in accordance with the *Declaration of Helsinki* and was approved by the local Ethics Committee of Wuhan Asia Heart Hospital (No. 2015-P-002). Informed written consent was obtained from all patients before their enrollment in this study.

Population

This was a prospective, observational, single-center trial. Patients over 18 years of age who were admitted to the coronary care unit of Wuhan Asia Heart Hospital presenting with STEMI between January 2015 and June 2015 were enrolled in this study. STEMI was diagnosed according to 2013 American College of Cardiology/American Heart Association (ACC/AHA) Guideline for the Management of STEMI.^[6] Exclusion criteria were age >75 years, serum creatinine >2.5 mg/dl, asthma, autoimmune diseases, pregnancy, malignancy, or patients unable to sign the informed consent form.

Detailed clinical data were obtained using a standardized questionnaire administered to the patient and treating physician at the time of the study, along with verification of medical records. All patients received standard treatment and were followed up for 12 months. Patients were divided into four groups according to their baseline sST2 (high baseline sST2 vs. low baseline sST2) levels and final therapeutic BB dose (high BB vs. low BB): low sST2 and low BB group, low sST2 and high BB group, high sST2 and low BB group, and high sST2 and high BB group. The incidences of total cardiovascular events were compared among the groups. The data including characteristics of the patients, procedures, echocardiography, and follow-up were managed by ResMan[®] (<http://www.medresman.org>).

Primary end point

The primary end point was a composite outcome defined as cardiovascular death, worsening HF (new or worsening symptoms/signs of HF requiring unplanned intensification of decongestive therapy), and recurrent MI through 1 year of follow-up. Recurrent MI was diagnosed if a patient had a plasma creatine kinase-MB (CK-MB) elevation greater than twice the normal value, or cardiac troponin I (cTNI) level above the 99th percentile for our population, and with at least

one of the following symptoms: chest pain lasting >20 min or diagnostic serial electrocardiographic changes consisting of new pathological Q waves or ST segment or T-wave changes. End points were ascertained through direct patient contact, medical records, and phone calls to patients or their family members.

Biomarkers

The prognostic cutoff value of sST2 in STEMI patients is undefined. Our previous study used 56 ng/ml as the threshold of risk for sST2,^[8] which was also used in the present analysis. Low baseline sST2 group was defined as baseline sST2 ≤56 ng/ml; high baseline sST2 group was defined as baseline sST2 >56 ng/ml. We designed a BB titration table according to the ACCF/AHA Guideline for the Management of STEMI.^[9] All patients without contraindication received BB titration treatment (metoprolol or metoprolol succinate). Median therapeutic BB dose was 50 mg of metoprolol or 47.5 mg of metoprolol succinate, which was used as a cutoff value to define high-dose BB therapy versus low-dose BB therapy.

Blood sample was obtained from each patient at the time of enrollment. Serum was isolated within 1 h of blood collection and stored at -80°C. sST2 was measured by a highly sensitive sandwich monoclonal immunoassay (Presage[®] ST2 Assay, Critical Diagnostics, New York). The intra- and inter-assay coefficients of variation were <4.0% and 2.5%, respectively. The lower limit of detection of sST2 was 3.1 ng/ml and the upper limit was 200 ng/ml. N-terminal prohormone B-type natriuretic peptide (NT-proBNP) was measured with Cobas e601 by a standard electrochemiluminescence immunoassay (Roche Diagnostics, Indianapolis, Indiana). The assay range was 20–5000 pg/ml. The intra- and inter-assay coefficients of variation were 2.9% and 6.1%, respectively. C-reactive protein (CRP) was measured with Beckman Coulter AU 5800, TNI with Beckman Coulter DXI 800, and creatinine with Beckman Coulter AU 5800. The estimated glomerular filtration rate (eGFR) was calculated from the simplified formula derived from the Modification of Diet in Renal Disease study.^[10]

Statistical analysis

Normally distributed continuous variables were summarized using mean ± standard deviation (SD), whereas nonnormality data were presented as median (25th, 75th percentile). Categorical variables were presented as counts and percentages. Categorical variables were compared between the four groups using the Chi-square test, and continuous variables were compared using analysis of variance (ANOVA) for symmetric continuous and Kruskal-Wallis test for nonsymmetric continuous data. Chi-square test was used to compare the incidence of total cardiovascular events between the four groups. The Kaplan-Meier test was used to analyze the effect of baseline sST2 value and final therapeutic BB dose on total cardiovascular

events. The log-rank test was used to compare survival curves. Univariable and multivariable Cox regression analyses were performed to determine the associations between baseline sST2 values, final achieved BB dose, and the presence of cardiovascular events. Multivariable models included covariates based on statistical evidence for confounding and/or clinical judgment. The multivariable model was initially created with both baseline sST2 status and final achieved BB dose status forced in, and then forward stepwise selection was used to choose the optimal predictors of cardiovascular events. Models for the continuous form of NT-proBNP, TNI, and CRP after lg transformation were also constructed. Variables considered for inclusion in the multivariable models were age, gender, smoking, baseline systolic blood pressure (SBP), heart rate, Killip Class, LV ejection fraction (LVEF), eGFR, lg NT-proBNP, lg TNI, lg CRP, and primary percutaneous coronary intervention (PPCI). Hazard ratio (HR) was determined from Cox regression models. In all statistical analyses, a two-tailed $P < 0.05$ was considered to indicate statistical significance. All analyses were performed with SPSS software version 20.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Baseline characteristics

Between January 2015 and June 2015, 186 patients were enrolled in our study. Mean age was 68.5 years (range: 30–72 years), and 64% of patients were men. Three patients with incomplete data were excluded, five patients were lost to follow-up (one patient in low baseline sST2 and low final BB dose group, two patients in low baseline sST2 and high final BB dose group, and two patients in high baseline sST2 and high final BB dose group), and the remaining 178 patients completed the 1-year follow-up.

The study cohort was divided into four groups according to the baseline sST2 (≤ 56 ng/ml vs. > 56 ng/ml) and final therapeutic BB dose (< 47.5 mg/d vs. ≥ 47.5 mg/d) [Table 1]. There were no significant differences in age, gender, and past medical history among the four groups. Patients with high baseline sST2 values who had low BB dosage had lower SBP levels but higher rate of Killip Class \geq II.

The biomarkers such as NT-proBNP, TNI peak, and CRP that are known to predict outcome after MI showed significant differences among the four groups. Patients with high baseline sST2 values who were not titrated to high BB dose had the highest baseline NT-proBNP concentration (2225.0 [976.3, 6095.0] pg/ml), whereas patients with low baseline sST2 values who were titrated to high-dose BB had the lowest baseline NT-proBNP values (210.5 [62.9, 1485.0] pg/ml). The other two groups had intermediate values. Similar patterns were observed in TNI and CRP. There were no statistically significant difference in eGFR and anterior MI [Table 1].

There was significant difference in baseline LVEF values ($P = 0.025$). The group with high baseline sST2 who were titrated to low BB dose had the lowest LVEF value (40.0 ± 8.7). There were no significant differences in the proportion of PPCI and involved vessel in these four groups [Table 1].

Baseline sST2 levels were positively correlated with heart rate ($r = 0.327$, $P = 0.002$), Killip Class ($r = 0.408$, $P = 0.000$), lg NT-proBNP ($r = 0.467$, $P = 0.000$), lg TNI ($r = 0.331$, $P = 0.000$), and lg CRP ($r = 0.307$, $P = 0.000$) and negatively correlated to SBP ($r = -0.243$, $P = 0.009$) and LVEF ($r = -0.402$, $P = 0.000$) [Table 2].

Cardiovascular events

There were a total of 28 end points in 27 patients in this study. The incidence of cardiovascular events during the 1-year follow-up was significantly different between the groups as stratified by baseline sST2 and final BB dosage [Figure 1, $P = 0.003$]. The lowest rate of 1-year major adverse cardiac event was seen in patients with low baseline sST2 values who were titrated to high-dose BB (6%) and intermediate rate in patients with low baseline sST2 who were not titrated to high-dose BB (8%) and patients with elevated sST2 titrated to high-dose BB (18%); the highest rate of events was seen in patients with high baseline sST2 who were not titrated to high BB dose (32%).

Death occurred in five patients: three (8%) patients in high baseline sST2 who were not titrated to high BB dose group (one patient who developed inferoposterior STEMI 2 days before admission to hospital suffered from cardiac rupture and died in the hospital; another patient with anterior STEMI suffered no-flow after PPCI treatment leading to death due to cardiogenic shock, whereas the third patient with anterior STEMI suffered sudden death due to unknown cause at home 10 days after PPCI treatment [a stent was implanted at proximal of the left anterior descending coronary artery, the patient recovered well and was discharged]). Two (4%) patients in elevated sST2 values titrated to high-dose BB group died. One patient with anterior STEMI and cardiogenic shock was referred to our hospital who received PPCI with intra-aortic balloon pump treatment and died 5 days later in the hospital due to low-output syndrome; another patient with inferoposterior STEMI without early revascularization underwent recurrent AMI 45 days later and died at a local hospital.

Recurrent MI occurred in three patients: one patient in low baseline sST2 not titrated to high-dose BB group, one patient with recurrent MI died as described above in the high baseline sST2 titrated to high-dose BB group, and one patient in high baseline sST2 not titrated to high-dose BB group. There was no significant difference among the groups ($P = 0.552$).

The number of patients with worsening HF in the four groups was three in the low baseline sST2 values who were titrated to high-dose BB group, two in the low baseline sST2 values who were not titrated to high-dose BB group, six in the high

Table 1: Baseline characteristics by sST2 and final achieved BB dose

Variables	Low sST2 (≤ 56 ng/ml)		High sST2 (> 56 ng/ml)		Statistic values	P
	Low BB (< 47.5 mg/d)	High BB (≥ 47.5 mg/d)	Low BB (< 47.5 mg/d)	High BB (≥ 47.5 mg/d)		
	(n = 37)	(n = 51)	(n = 40)	(n = 50)		
Age, years	61.8 \pm 6.4	62.6 \pm 7.5	61.6 \pm 5.6	64.0 \pm 5.7	1.347*	0.261
Male	28 (75.7)	39 (73.6)	30 (75.0)	36 (75.0)	0.073†	0.996
Past medical history						
Hypertension	23 (62.2)	33 (62.3)	23 (57.5)	28 (58.3)	0.368†	0.951
Diabetes	8 (21.6)	13 (24.5)	7 (17.5)	13 (27.1)	1.015†	0.743
Current smoker	28 (75.7)	33 (62.3)	29 (72.5)	27 (56.3)	0.216†	0.200
Examination						
BMI (kg/m ²)	25.2 \pm 3.6	26.3 \pm 3.1	26.1 \pm 2.6	26.7 \pm 3.5	1.619*	0.132
SBP (mmHg)	131.4 \pm 22.4	139.3 \pm 25.3	117.4 \pm 17.6	132.7 \pm 27.8	6.067*	0.000
Heart rate (beats/min)	70.0 \pm 12.6	81.1 \pm 18.7	77.5 \pm 23.9	82.7 \pm 18.4	2.228*	0.093
Killip class \geq II	2 (5.4)	9 (16.9)	12 (30.0)	13 (27.1)	8.649†	0.034
Laboratory results						
NTproBNP	1063.0 (233.1, 1946.0)	210.5 (62.9, 1485.0)	2225.0 (976.3, 6095.0)	1584.0 (549.3, 4155.0)	31.05†	0.000
TNI	20.2 (2.7, 54.3)	31.6 (4.52, 78.8)	62.4 (27.8, 137.6)	53.8 (16.9, 132.3)	11.00†	0.012
CRP	2.7 (0.7, 6.2)	3.1 (0.9, 18.1)	11.2 (2.2, 62.6)	7.8 (2.0, 58.0)	12.18†	0.006
eGFR (ml·min ⁻¹ ·1.73m ⁻²)	93.0 \pm 28.3	95.8 \pm 28.7	85.4 \pm 34.8	101.8 \pm 34.1	1.711*	0.153
Anterior MI	19 (51.3)	31 (58.5)	31 (77.5)	33 (68.6)	6.052†	0.109
LVEF	46.4 \pm 5.6	45.2 \pm 7.8	40.0 \pm 8.7	43.7 \pm 5.5	5.685*	0.025
Primary PCI	27 (72.9)	39 (76.4)	25 (62.5)	37 (74.0)	2.427†	0.489
Culprit vessel						0.705
Left main coronary artery	0	0	2 (8.0)	1 (2.7)	–	–
Left anterior descending coronary artery	15 (55.6)	20 (51.3)	11 (44.0)	21 (56.8)	–	–
Left circumflex coronary artery	4 (14.8)	8 (20.5)	5 (20.0)	6 (16.2)	–	–
Right coronary artery	8 (29.6)	11 (28.2)	7 (28.0)	9 (24.3)	–	–
Final meds						
BB	37 (100)	51 (100)	31 (77.5)	42 (84.0)	12.17†	0.000
ACE	23 (62.2)	35 (68.6)	14 (35.0)	24 (48.0)	11.92†	0.008
ARB	3 (8.1)	5 (9.8)	3 (7.5)	4 (8.0)	0.027†	0.869
MRA	2 (5.4)	6 (11.7)	9 (22.5)	8 (16.0)	5.034†	0.169
Statins	37 (100)	51 (100)	40 (100)	50 (100)	–	–
Dual antiplatelet drugs	37 (100)	51 (100)	40 (100)	50 (100)	–	–

Values were shown as mean \pm standard deviation, median (25th, 75th percentile), or n(%). *F values; † χ^2 values. BMI: Body mass index; NTproBNP: N-terminal pro-hormone B-type natriuretic peptide; CRP: C-reactive protein; eGFR: Estimated glomerular filtration rate; LVEF: Left ventricular ejection fraction; ACE: Angiotensin-converting enzyme; ARB: Angiotensin receptor blockers; MRA: Mineralocorticoid receptor antagonists; BB: Beta-blockers; sST2: Soluble ST2; SBP: Systolic blood pressure; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; TNI: Troponin I; –: Data not applicable.

Table 2: Correlation between ST2 and continuous variables

Variables	Spearman's r	P
Age	-0.002	0.896
SBP	-0.243	0.009
Heart rate	0.327	0.002
eGFR	-0.06	0.429
Killip class	0.408	0.000
LVEF	-0.402	0.000
Lg NTproBNP	0.467	0.000
Lg TNI	0.331	0.000
Lg CRP	0.307	0.000

eGFR: Estimated glomerular filtration rate; LVEF: Left ventricular ejection fraction; NTproBNP: N-terminal pro-hormone B-type natriuretic peptide; CRP: C-reactive protein; SBP: Systolic blood pressure; TNI: Troponin I.

baseline sST2 values who were titrated to high-dose BB group, and nine in the high baseline sST2 values who were

not titrated to high-dose BB group. There was a significant difference among the groups ($P = 0.049$).

Kaplan-Meier analysis and predictors of cardiovascular events

In the Kaplan-Meier analysis [Figure 2, $P < 0.0001$], the highest risk with time was for patients with highest baseline sST2 concentrations who were not titrated to high-dose BB therapy. Patients with low baseline sST2 values who were titrated to high-dose BB or not titrated to high-dose BB had similar outcomes but low consequent risk of cardiovascular events with time. Patients with high baseline sST2 values titrated to high-dose BB were at intermediate risk.

Furthermore, univariate and multivariate Cox regression analyses were performed to identify the associations between baseline sST2 values, final achieved BB dose, and the presence of cardiovascular events. Univariate

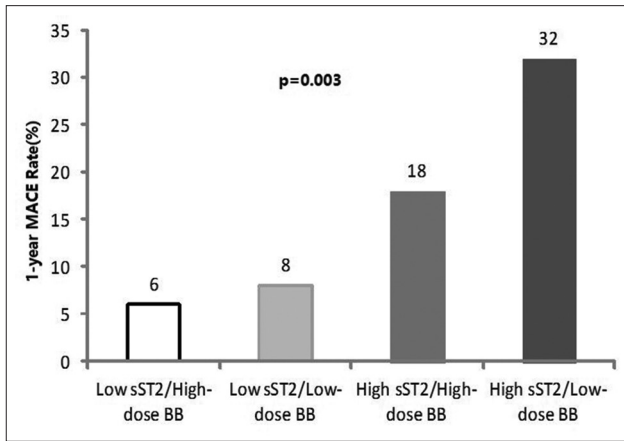


Figure 1: One-year incidence of cardiovascular events (%) by baseline sST2 values and final BB dosage. BB: Beta-blockers; sST2: Soluble ST2.

Cox regression analysis indicated that baseline SBP (*HR*: 1.033; 95% confidence interval [*CI*]: 1.010–1.057; *P* = 0.006), baseline heart rate (*HR*: 0.997; 95% *CI*: 0.978–1.017; *P* = 0.042), lg NTproBNP (*HR*: 1.592; 95% *CI*, 0.685–3.699; *P* = 0.047), baseline high sST2 status (*HR*: 2.317; 95% *CI*: 1.381–6.095; *P* = 0.005), final low BB status (*HR*: 2.109; 95% *CI*: 1.017–5.272; *P* = 0.046), and *PPCI* (*HR*: 0.444; 95% *CI*: 0.214–0.923; *P* = 0.030) were correlated with cardiovascular events. Multivariate Cox regression analysis showed that baseline SBP (*HR*: 1.044; 95% *CI*: 1.023–1.066; *P* = 0.000), lg NTproBNP (*HR*: 1.943; 95% *CI*: 1.003–3.765; *P* = 0.049), baseline high sST2 status (*HR*: 2.653; 95% *CI*: 1.201–8.929; *P* = 0.041), and final low BB status (*HR*: 1.904; 95% *CI*: 1.084–3.053; *P* = 0.035) were independent risk factors for cardiovascular events [Table 3].

DISCUSSION

The present study showed that an elevated level of baseline sST2 and final low BB dose were predictors of cardiovascular events through 1 year in STEMI, independent of NTproBNP, and baseline SBP. Baseline sST2 measurement identifies patients with STEMI who may particularly benefit from higher BB doses. Those with highest risk for cardiovascular events were identified by an elevated baseline sST2 value, but this risk was not entirely obvious in those titrated to higher dose BB. Hence, higher dose BB therapy may be particularly efficacious in patients with an elevated sST2.

sST2 was positively correlated with heart rate, Killip Class, lg NTproBNP, lg TNI, and lg CRP and negatively correlated with SBP and LVEF. In Weir *et al.* study, the sST2 levels were measured in 100 patients admitted with AMI and resultant LV systolic dysfunction, and all patients underwent cardiac magnetic resonance imaging at baseline and at 12 and 24 weeks. The results showed that serum sST2 correlated significantly with LVEF at baseline ($r = -0.30$, $P = 0.002$) and 24 weeks ($r = -0.23$, $P = 0.026$); level of sST2 was positively associated with infarct volume index at baseline ($r = 0.26$, $P = 0.005$) and 24 weeks

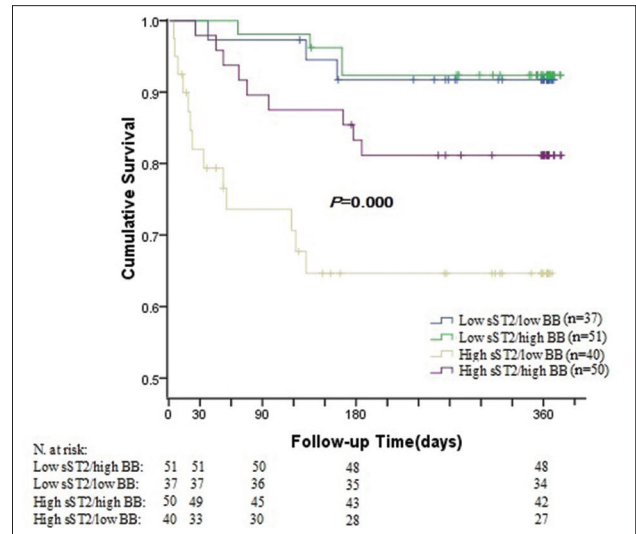


Figure 2: Kaplan-Meier analysis by baseline sST2 and final BB dosage. BB: Beta-blocker; sST2: Soluble ST2.

Table 3: Cox regression analysis of cardiovascular events

Variables	<i>HR</i>	95% <i>CI</i>	<i>P</i>
Univariate Cox regression analysis			
Age	0.255	0.098–0.663	0.677
Male	0.463	0.108–1.989	0.835
Baseline SBP	1.033	1.010–1.057	0.006
Baseline heart rate	0.997	0.978–1.017	0.042
Killip class \geq II	1.033	0.721–1.830	0.956
LVEF	1.149	0.943–1.061	0.935
eGFR	1.000	0.983–1.004	0.085
Lg NTproBNP	0.994	0.685–3.699	0.047
Lg TNI	1.592	0.808–2.756	0.277
Lg CRP	1.492	0.644–2.229	0.772
Baseline high sST2 status	1.198	1.381–6.095	0.005
Final low BB status	2.317	1.017–5.272	0.046
Primary <i>PCI</i>	0.444	0.214–0.923	0.030
Multivariate Cox regression analysis			
Baseline SBP	1.044	1.023–1.066	0.000
Lg NTproBNP	1.943	1.003–3.765	0.049
Baseline high sST2 status	2.653	1.041–6.764	0.041
Final low BB status	1.904	1.084–3.053	0.035

LVEF: Left ventricular ejection fraction; eGFR: Estimated glomerular filtration rate; NTproBNP: N-terminal prohormone B-type natriuretic peptide; *HR*: Hazard ratio; *CI*: Confidence interval; BB: Beta-blockers; sST2: Soluble ST2; SBP: Systolic blood pressure; CRP: C-reactive protein; *PCI*: Percutaneous coronary intervention; TNI: Troponin I.

($r = 0.22$, $P = 0.037$).^[5] In Shimpo *et al.* study, sST2 levels were measured in 810 patients with AMI, and baseline sST2 levels were found to be positively correlated with the time to randomization, heart rate, CK-MB peak, cTNI, and CRP. These results consistently demonstrated the relationship between sST2 and clinical variables.

In Shimpo's prior study, ST2 levels were anticipated to increase on the 1st day after coronary occlusion and return to

normal over the next 14 days.^[4] Among the 14 thrombolysis in MI patients, analysis of serial measurements of serum ST2 in 228 patients revealed an increase with time, with most patients reaching a peak ST2 level at 12 h. Accordingly, sST2 levels at baseline rather than subsequent values appeared to be more predictive of risk of cardiovascular death or HF.^[11] Hence, in our study, we only observed the relationship between baseline sST2 and cardiovascular events.

We found that SBP levels were significantly lower in patients who were not titrated to higher BB dose, which may partly explain why such titration did not occur in clinical setting. There was no significant difference in heart rate or PPCI between the four groups. Although patients with high baseline sST2 values had higher percentage of Killip Class \geq II, lower LVEF, and higher TNI or CRP level, in multivariable Cox regression model analysis, the differences in Killip Class \geq II, LVEF, TNI, or CRP were not significant in the prediction of cardiovascular events. Baseline SBP, NTproBNP level, baseline high sST2 status, and final low BB status were significant in predicting cardiovascular events. The relationship between ST2 and NT-proBNP levels was unclear. Zhang *et al.*^[12] revealed that serum sST2 levels correlated with cardiovascular death or HF in a dose-dependent manner and may provide complementary information to NT-proBNP.

The association between sST2 and BB therapy requires in-depth study. Cardiac remodeling is a central feature in the development and progression of STEMI, a process that includes hypertrophy and apoptosis of cardiomyocytes, reinduction of fetal gene expression, and alterations in the extracellular matrix including fibroblasts.^[13] One of the critical factors in cardiac remodeling is the primary sympathetic neurotransmitter norepinephrine that acts through α - and β -adrenergic receptors and is thought to play a central role in initiating and sustaining cardiac remodeling. Acting directly through the β -adrenergic receptors, BBs block the activation of the sympathetic nervous system and deter progression of STEMI through inhibiting adverse remodeling.^[14,15] sST2 is markedly induced in mechanically overloaded cardiomyocytes and is intimately involved in cardiac remodeling.^[11] sST2 was elevated *in vivo* after experimental AMI in mice and was also shown to be elevated in the serum of patients after AMI.^[16] The role of sST2 in remodeling seems to be mediated by its effect on its primary ligand, IL-33, which itself is also synthesized when cardiac fibroblasts are mechanically stretched. IL-33 has been shown to inhibit cardiomyocyte hypertrophy, fibrosis, and apoptosis.^[17] How BB may influence this complex physiology remains unclear and needs further study.

Weir *et al.*^[18] showed that sST2 measurement may identify patients after MI who are most likely to show beneficial LV remodeling with mineralocorticoid receptor antagonists therapy. Gaggin *et al.*^[7] suggested that sST2 measurement can identify patients with chronic HF who may particularly benefit from higher BB doses. A similar relationship between BB therapy and sST2 value was found in the present study.

sST2 may potentially be used to identify specific therapies for the efficient management of STEMI or HF. More information about sST2 at molecular and cellular levels are needed to confirm the association with LV remodeling and prognosis in STEMI.

Potential limitations of this study merit consideration. First, this was an observational single-center study with a small number of participants. Second, the number of patients titrated to goal doses of BB was small. However, our results support that sST2 identified risk even in patients titrated to highest dose BB.

In conclusion, our study showed that sST2 values could identify different strata of risk based on final BB doses. These data offer the possibility of prospectively exploring the use of sST2-guided BB therapy in STEMI patients.

Financial support and sponsorship

This work was supported by grants from Beijing Lisheng Cardiovascular Health Foundation (No. LSG2014-2015) and Wuhan innovational funding (No. WX16E31).

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Tominaga Si, Kuroiwa K, Tago K, Iwahana H, Yanagisawa K, Komatsu N, *et al.* 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. doi: 10.1006/bbrc.1999.1469.
2. Weinberg EO, Shimpo M, De Keulenaer GW, MacGillivray C, Tominaga S, Solomon SD, *et al.* Expression and regulation of ST2, an interleukin-1 receptor family member, in cardiomyocytes and myocardial infarction. *Circulation* 2002;106:2961-6. doi: 10.1161/01.CIR.0000038705.69871.D9.
3. Demyanets S, Speidl WS, Tentzeris I, Jarai R, Katsaros KM, Farhan S, *et al.* Soluble ST2 and interleukin-33 levels in coronary artery disease: Relation to disease activity and adverse outcome. *PLoS One* 2014;9:e95055. doi: 10.1371/journal.pone.0095055.
4. Shimpo M, Morrow DA, Weinberg EO, Sabatine MS, Murphy SA, Antman EM, *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. doi: 10.1161/01.CIR.0000127958.21003.5A.
5. Weir RA, Miller AM, Murphy GE, Clements S, Steedman T, Connell JM, *et al.* Serum soluble ST2: A potential novel mediator in left ventricular and infarct remodeling after acute myocardial infarction. *J Am Coll Cardiol* 2010;55:243-50. doi: 10.1016/j.jacc.2009.08.047.
6. American College of Emergency Physicians; Society for Cardiovascular Angiography and Interventions, O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr., *et al.* 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;61:e78-140. doi: 10.1016/j.jacc.2012.11.019.
7. Gaggin HK, Motiwala S, Bhardwaj A, Parks KA, Januzzi JL Jr. Soluble concentrations of the interleukin receptor family member ST2 and β -blocker therapy in chronic heart failure. *Circ Heart Fail* 2013;6:1206-13. doi: 10.1161/CIRCHEARTFAILURE.113.000457.
8. Lei H, Jian P, Xuan Z, Fang L, Chengwei L, Mingxiang W, Xi S. Serum levels of soluble ST2 associated with clinical outcome in ST-elevation myocardial infarction (in Chinese). *Chin Circ J* 2017;32:41-5. doi: 10.3969/j.issn.1000-3614.2017.01.010.
9. Lei H, Fang L, Chengwei L, Mingxiang W, Xi S, Min L, Bao Y.

- Titration of beta-blockers in patients with ST-elevation myocardial infarction (in Chinese). *J Clin Cardiol* 2016;32:681-4. doi: 10.13201/j.issn.1001-1439.2016.07.008.
10. Smilde TD, van Veldhuisen DJ, Navis G, Voors AA, Hillege HL. Drawbacks and prognostic value of formulas estimating renal function in patients with chronic heart failure and systolic dysfunction. *Circulation* 2006;114:1572-80. doi: 10.1161/CIRCULATIONAHA.105.610642.
 11. Sabatine MS, Morrow DA, Higgins LJ, MacGillivray C, Guo W, Bode C, *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. doi: 10.1161/CIRCULATIONAHA.107.728022.
 12. Zhang K, Zhang XC, Mi YH, Liu J. Predicting value of serum soluble ST2 and interleukin-33 for risk stratification and prognosis in patients with acute myocardial infarction. *Chin Med J* 2013;126:3628-31. doi: 10.3760/cma.j.issn.0366-6999.20130145.
 13. Colucci WS. Molecular and cellular mechanisms of myocardial failure. *Am J Cardiol* 1997;80:15L-25L. doi: 10.1016/S0002-9149(97)00845-X.
 14. Metoprolol in acute myocardial infarction (MIAMI). A randomised placebo-controlled international trial. The MIAMI trial research group. *Eur Heart J* 1985;6:199-226. doi: 10.1093/oxfordjournals.eurheartj.a061845.
 15. Yusuf S, Wittes J, Friedman L. Overview of results of randomized clinical trials in heart disease. I. Treatments following myocardial infarction. *JAMA* 1988;260:2088-93. doi: 10.1001/jama.260.14.2088.
 16. Weinberg EO, Shimpo M, Hurwitz S, Tominaga S, Rouleau JL, Lee RT, *et al.* Identification of serum soluble ST2 receptor as a novel heart failure biomarker. *Circulation* 2003;107:721-6. doi: 10.1161/01.CIR.0000047274.66749.FE.
 17. Seki K, Sanada S, Kudinova AY, Steinhauser ML, Handa V, Gannon J, *et al.* Interleukin-33 prevents apoptosis and improves survival after experimental myocardial infarction through ST2 signaling. *Circ Heart Fail* 2009;2:684-91. doi: 10.1161/CIRCHEARTFAILURE.109.873240.
 18. Weir RA, Miller AM, Murphy GE, Clements S, Steedman T, Connell JM, *et al.* Serum soluble ST2: A potential novel mediator in left ventricular and infarct remodeling after acute myocardial infarction. *J Am Coll Cardiol* 2010;55:243-50. doi: 10.1016/j.jacc.2009.08.047.

血清可溶性ST2水平、 β 受体阻滞剂治疗与ST段抬高型心肌梗死患者预后的关系

摘要

背景: 有研究发现血清可溶性ST2 (sST2) 水平在急性心肌梗死发生早期升高, 同时与ST段抬高型心肌梗死 (STEMI) 患者的左心室重构及预后相关。 β 受体阻滞剂通过改善STEMI患者左心室重构进而改善预后。本研究初步探讨了STEMI患者中基线sST2水平, β 受体阻滞剂剂量与预后的关系。

方法: 2015年1月至6月于武汉亚洲心脏病医院纳入符合标准的186名STEMI患者。所有患者接受正规治疗并随访至1年。测量患者基线血清sST2水平。依据基线sST2水平 (高sST2 > 56 ng/ml vs. 低sST2 \leq 56 ng/ml) 及最终 β 受体阻滞剂的治疗剂量 (高剂量组 \geq 47.5mg vs. 低剂量组 < 47.5) 分为4组。应用Cox回归分析确定sST2水平、BB剂量在STEMI患者中的预测价值。

结果: 基线sST2水平与心率 ($r=0.327, p=0.002$)、Killip class ($r=0.408, p=0.000$)、lgNTproBNP ($r=0.467, p=0.000$)、lgTnI ($r=0.331, p=0.000$) 和 lgCRP ($r=0.307, p=0.000$) 正相关, 与SBP ($r=-0.243, p=0.009$) 和 LVEF ($r=-0.402, p=0.000$) 负相关。基线sST2升高伴低剂量BB的患者预后较差 ($p=0.000$)。基线高sST2水平 (HR, 2.653; 95% CI, 1.201-8.929; $p=0.041$) 及低剂量BB (HR, 1.904; 95% CI, 1.084-3.053; $p=0.035$) 是STEMI患者出现心血管事件的独立预测因素。

结论: 基线高sST2水平及低剂量BB是STEMI患者出现心血管事件的独立预测因素, sST2 可能是心脏病理生理过程的一个有用生物标记物。