Original Article

Combined use of high-sensitivity ST2 and NT-proBNP for predicting major adverse cardiovascular events in coronary heart failure

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Background: Elevated serum soluble ST2 (sST2) level is marker of poor prognosis in chronic heart failure (HF). N-terminal pro-brain natriuretic peptide (NT-proBNP) is an important biomarker in cardiovascular diseases. This study aimed to address the incremental usefulness of the combined use of high-sensitivity sST2 and NT-proBNP for predicting the risk of major adverse cardiovascular events (MACEs) in patients with coronary heart disease (CHD).

Methods: We used patient data along with data established by our research group to compare the performance of a combination of biomarkers reflecting ventricular fibrosis, remodeling, stretch and deterioration of cardiac function (sST2 and NT-proBNP) with that of established mortality risk factors [age, diabetes, systolic blood pressure, diastolic blood pressure, left ventricular ejection fraction (LVEF), body mass index (BMI), creatinine (Cr), uric acid (UA), glucose (Glu)] in stratifying the risk of MACEs in CHD patients.

Results: The median follow-up period was 3.9 years, during which time there were 3,724 cases with CHD, 113 cases of cardiovascular death, 30 cases with myocardial infarction, 49 cases with stroke, 39 cases of non-cardiovascular death, 6 cases of peripheral arterial occlusion, 55 cases with HF, and 73 cases of revascularization. A total of 365 cases had MACEs. In the multivariate Cox proportional hazard model, both sST2 and NT-proBNP were significant predictors of MACEs. Both sST2 and NT-proBNP were separately incorporated into the model with established MACE risk factors, which significantly improved the C-statistics for predicting MACEs [0.758 (0.724–0.792)] and saw an estimated net improvement in reclassification of 1.03% ($P<0.001$) and an integrated discrimination improvement of 0.48% ($P<0.001$). The Hosmer-Lemeshow test showed that the models were well calibrated with and without the two biomarkers ($P>0.344$ for all comparisons). Moreover, the model incorporating the two biomarkers was shown to have a better global fit than the model with only the established MACE risk factors ($P<0.001$).

Conclusions: A model incorporating sST2 and NT-proBNP was shown to outperform a model based on established MACE risk factors alone in stratifying risk of MACEs in a group of CHD patients.

Keywords: Coronary heart disease (CHD); soluble ST2 (sST2); N-terminal pro-brain natriuretic peptide (NT-proBNP); major adverse cardiovascular events (MACEs)

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Introduction

Coronary heart disease (CHD) is an inflammatory process mediated by many cytokines involved in innate and acquired immune activities (1). The participation of the interleukin (IL)-33/IL-1 receptor-like 1 (IL-33/ST2) axis in many cardiovascular diseases has been revealed in previous studies (2-8). These findings suggest that a novel mechanism of intramyocardial fibroblast-myocyte communication leads to ventricular remodeling and myocyte apoptosis. Moreover, an elevated serum soluble ST2 (sST2) level has been shown to be a significant marker of poor prognosis in both chronic heart failure (HF) (9,10) and acute myocardial infarction (11,12). A correlation has also been identified between plasma sST2 and many other cardiovascular biomarkers or hormones, including B-type natriuretic peptide (BNP), N-terminal pro-brain natriuretic peptide (NT-proBNP), C-reactive protein (CRP), troponin T, creatine kinase, IL-6, noradrenaline, and aldosterone (13).

BNP is expressed by the myocardium in response to elevated atrial wall pressure and reduces venous return to the heart by influencing the vascular endothelium and the kidneys and suppressing reflex sympathetic activation (14,15). ProBNP is the active form of BNP in circulation (16). BNP and NT-proBNP have become important biomarkers in cardiovascular disease (17-20), including for acute coronary syndrome (ACS) and stable coronary artery disease (21-37).

In a study by the Northern New England Cardiovascular Disease Study Group, a full prediction model that included NT-proBNP and sST2 demonstrated significantly improved classification of in-hospital mortality in patients who received coronary artery bypass graft (CABG) in comparison with the Northern New England (NNE) model alone (38). Meanwhile, the Fragmin and fast Revascularization during InStability in Coronary artery disease (FRISC) II trial showed that NT-proBNP level could be used to identify patients who would benefit most from invasive treatment at an early point, particularly when used in combination with inflammatory factors such as IL-6 (39). High-sensitivity cardiac troponin T (hs-cTnT) and NT-proBNP were included in a multivariate model which showed higher discrimination ability in predicting mortality than the model without biomarkers (40). By combining hs-cTnT and NT-proBNP, the long-term (four-year) prediction of mortality risk in patients with stable CHD can be improved (41-43). NT-proBNP, hs-cTnT, and low-density lipoprotein cholesterol (LDL-C) are the three most significant biomarkers, and NT-proBNP and hs-cTnT possess superior value to other clinical biomarkers or variables (smoking, diabetes mellitus, and peripheral arterial disease) as predictors of cardiovascular death in patients with stable CHD.

Therefore, taking the roles of inflammatory and myocardial stretch in CHD into account, we hypothesized that a combination of sST2 and NT-proBNP might offer superior valuable in predicting the risk of major adverse cardiovascular events (MACEs) in CHD patients. To test this hypothesis, we performed an association analysis of sST2, NT-proBNP, and CHD risk in a case control study in patients from the Department of Cardiology of PLA General Hospital.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/apm-20-1046).

Methods

Study population

The study included patients with CHD confirmed by coronary angiography who were hospitalized in the Department of Cardiology of PLA General Hospital between January 2007 and January 2017. The requirement for informed consent was waived as the data of patients involved in this study were retrospectively analyzed. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study received approval from the ethical review committee of the PLA General Hospital (S2016-070-02).

The inclusion criteria were as follows (3,5,8,9,12,17): (I) age ≥30 years; (II) experienced an episode of ischemic discomfort lasting a minimum of 30 minutes within 6 hours before admission; (III) exhibited at least 0.1-mV ST-segment elevation in 2 contiguous electrical cardiogram (ECG) leads; and (IV) willing and able to provide written informed consent.

The exclusion criteria were as follows (3,5,8,9,12,17): (I) evidence of cardiogenic shock; (II) serum creatinine (Cr) ≥1,300 μmol/L; (III) end-stage renal disease requiring dialysis; (IV) unable to follow the protocol or follow-up; (V) unable or unwilling to provide informed consent; (VI) a lack of samples for sST2 measurement; or (VII) any condition that might reduce the possibility of collecting the data needed to meet the study objectives. Blood samples were obtained from the patients by venipuncture and centrifuged before being stored at −80 ℃. The same blood sample was used to determine NT-proBNP and sST2 levels.

Follow-up and outcome

Each patient was regularly followed up. When decompensation occurred, additional follow-up visits were made. In general, the patients were visited by nurses on a quarterly basis and by physician biannually. They also received elective follow ups from cardiologists, psychiatrists, and rehabilitation physicians. Patients who did not receive visits regularly were instead followed up via telephone. The follow-up procedure comprised a standard postal or telephone questionnaire to assess events such as death and acute myocardial infarction (AMI). When events were suspected to have occurred, the patients' medical reports were obtained from treatment facilities or primary physicians and their case files were reviewed. MACEs in this study included major endpoint events, such as coronary revascularization, cardiovascular death, myocardial infarction, cerebral infarction/cerebral hemorrhage, non-cardiovascular death, peripheral arterial occlusion (extremities, kidney, and carotid artery), and HF.

sST2 assay

Measurements of sST2 were obtained from the stored serum samples with a high-sensitivity sandwich monoclonal immunoassay (Presage® ST2 assay, Critical Diagnostics, San Diego, CA, USA), which can accurately quantify sST2 levels, especially at low concentrations. For the Presage assay, the recombinant protein was used to generate antibodies based on the human cDNA clone for the complete sST2 sequence. The within-run coefficient of the sST2 assay was <2.5%, and the total coefficient of variation was 4%.

NT-proBNP assay

A standard electrochemiluminescence immunoassay (Elecsys proBNP, Roche Diagnostics, Indianapolis, IN) was used to measure serum NT-proBNP, as previously described (16). The range of the assay was 20 to 5,000 pg/mL, and it had intra- and inter-assay coefficients of variation of 2.9% and 6.1%, respectively. The measurement of NT-proBNP level was obtained from the same sample for sST2 level testing.

Statistical analysis

Categorical variables were compared using the χ^2 or Fisher's exact tests and expressed as percentages. Continuous variables were compared by Student's *t*-test or the Mann-Whitney U test and expressed as the mean (standard deviation) or median (interquartile range) based on normal or non-normal distribution respectively. Associations between sST2 and NT-proBNP tertiles and relevant clinical variables were analyzed with analysis of variance (ANOVA) and Kruskal-Wallis test for symmetrical and asymmetrical continuous variables, respectively, and with χ^2 test for categorical variables.

The association between MACEs and age, blood pressure, left ventricular ejection fraction (LVEF), body mass index (BMI), Cr, uric acid (UA), glucose (Glu), high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), total cholesterol (TC), triglyceride (TG), growth differentiation factor (GDF)-15, fibrinogen, Comorbidity, CHD type, multivessel disease, smoking, and treatment was analyzed using the Cox regression model. The assumption of linearity of the covariables sST2 and NT-proBNP was fulfilled using a quadratic term of sST2 and the logarithmic function of NT-proBNP in the Cox models.

The optimal cut-off points for sST2 and NT-proBNP were determined with ROC curvilinear coordinates and the tangent coordinates = sensitivity – (1-specificity), where the longitudinal axis was sensitivity and the transverse axis was 1-specificity.

The potential value of the inclusion of these biomarkers for predicting MACEs was assessed using three different forms of statistical analysis. In the bivariate regression analysis, the models were assessed for goodness of fit by applying the Hosmer-Lemeshow test, and the concordance index (C-statistic) was computed to compare the improvement in the discrimination ability of the sST2 and NT-proBNP biomarker model with that of the model without them. In binary regression analysis, the probability of MACEs of covariate was calculated based on statistically significant variables of risk factors for MACE from the COX regression analysis. In receiver operation curve (ROC) curve analysis, variables of risk factors, along with + sST2, + NT-proBNP, + ST2 and NT-proBNP serve as test variables, and MACEs as state variables to conduct the C-statistic.

Reclassification was mainly assessed using two statistics. First, net reclassification improvement (NRI) needed meaningful risk categories to be defined (tertiles of sST2 and BNP for the risk of MACEs were used). NRI was used to determine the incremental value of sST2, NT-proBNP, and sST2 + NT-proBNP including the variables for the prediction of outcomes at 3.9 years (42,43). NRI took into account changes in the estimated MACE prediction

probabilities that implied a change between two categories. Second, integrated discrimination improvement (IDI) viewed the changes in the estimated MACE prediction probabilities as continuous variables. IDI = $[(P_{new,\ events} - P_{old,\ events}) - (P_{new,\ non\text{-}events} - P_{old,\ non\text{-}events})]$.

The fitness information of the model with the two biomarkers was tested by likelihood ratio test in the multiple logistic regression analysis, with MACEs as dependent variables, and the variables with statistically significant differences between MACEs and non-MACEs as covariates.

Statistical significance was indicated by two-sided P values of <0.05. SPSS (version 18.0 for Windows, SPSS, Inc., Chicago, IL, USA) statistical package was used to perform all statistical analyses.

Results

Baseline characteristics

Data from 1,113 consecutive patients were analyzed in this study. The median age of the patients was 65 years (range, 32–95 years) old. The baseline characteristics of the included patients are shown in *Table 1*. In summary, the follow-up period lasted 3.9 years, during which time there were 113 cases of cardiovascular death, 30 cases of myocardial infarction, 49 cases of stroke, 39 cases of non-cardiovascular death, 6 cases of peripheral arterial occlusion, 55 cases of HF, and 73 cases of revascularization. A total of 365 cases had MACEs.

In Cox regression analysis, age, DBP, LVEF, BMI, Cr, UA, fibrinogen, NT-proBNP, and sST2 were found to be statistically significant continuous variables, while stroke, hypertension, hyperlipidemia, and diabetes were shown to be statistically significant categorical variables (P all <0.05). The treatment methods with statistical significance were aspirin, statins, beta blocker, revascularization, and PCI.

Cox regression and modelling

Cox regression analysis showed that age, NT-proBNP, systolic blood pressure (SBP), sST2, TC, CABG, EF, aspirin, UA, fibrinogen, and hypertension were significant independent predictors of MACEs. In the Cox regression analysis, NT-proBNP [hazard ratio (HR): 1.000024; 95% confidence interval (CI): 1.000011–1.000036; P<0.001] and sST2 (HR: 1.010; 95% CI: 1.001–1.018; P<0.05) were predictors of MACEs (*Table 2*).

The best cut-off points for sST2 (43.7 ng/mL; 95% CI: 19.7–60.2; *Figure 1A*) and NT-proBNP (1,594.5 ng/mL; 95% CI: 85.4–17,864.4; *Figure 1B*) for predicting prognosis were identified by ROC curvilinear coordinates and the tangent coordinates. The patients were divided into four subgroups based on the aforementioned sST2 and NT-proBNP cut-off points, to establish to potential value of simultaneously assessing sST2 and NT-proBNP. The risk of MACEs in patients who had elevated levels of sST2 or NT-proBNP was higher than that in the reference group with low levels of each marker (*Figure 2*). Meanwhile, the risk for patients with elevated levels of both sST2 and NT-proBNP was markedly higher again. These results suggest that sST2 and NT-proBNP can more effectively identify patients who are at high risk of developing MACE when assessed in combination than when either one of these biomarkers is assessed alone.

Discrimination

The model with established MACEs risk factors (age, NT-proBNP, SBP, sST2, TC, CABG, EF, Aspirin, UA, fibrinogen, hypertension) had a C-statistic value of 0.742 (P<0.001). When separately incorporated into the model, NT-proBNP and sST2 both led to a significant improvement in the C-statistic for the prediction of MACEs of any cause (0.756 and 0.745 respectively). Furthermore, the model with the established MACEs risk factors that incorporated both biomarkers saw a significant increase in the C-statistic for predicting MACEs (*Table 3*).

Reclassification

MACEs patients were reclassified by risk category based on the occurrence of MACE during the follow-up period (*Table 4*). Following the separate inclusion of sST2, the model with established MACE risk factors and NT-proBNP, had an NRI of 1.03% (P<0.001), and an IDI = [(42.17–41.82) – (21.44–21.57)] of 0.48% (P<0.001). The NRI for patients who experienced MACEs was 0.66% (P<0.001), and the NRI for survivors was 0.37% (P<0.001) (*Tables 4-7*).

Calibration

The Hosmer-Lemeshow test was performed to determine the goodness of fit of the models. The results indicated that the models with and without the two biomarkers were well calibrated (P=0.355 *vs.* P=0.344).

Table 1 Demographic and clinical baseline characteristics and treatment during follow-up

Items	MACE free (n=748)	MACE (n=365)	t/X^2 value	P value
Age, years	63.07±11.72	68.61±12.56	–6.88	<0.001
SBP, mmHg	136.55±29.58	136.28±23.92	0.14	0.887
DBP, mmHg	76.23±27.61	72.55±12.37	2.23	0.026
EF, %	54.98±8.61	49.90±11.20	7.12	<0.001
BMI, kg/m^2	25.39±3.38	24.89±3.72	2.15	0.032
Creatinine, μmol/L	90.25±80.45	130.27±138.41	–4.73	<0.001
UA, μmol/L	337.30±99.96	393.29±310.77	–3.07	0.002
Glucose, mmol/L	7.04±2.90	7.35±3.42	–1.39	0.166
HDL-C, mmol/L	1.07±0.32	1.05±0.31	0.89	0.376
LDL-C, mmol/L	2.41±0.91	2.40±1.02	0.05	0.957
GDF-15, pg/mL	2,778.00±2,089.06	4,036.96±2,656.08	–7.42	<0.001
Fibrinogen, g/L	3.38±0.98	3.95±1.36	–6.73	<0.001
TC, mmol/L	4.03±1.07	4.02±1.11	0.20	0.845
TG, mmol/L	1.48±0.86	1.38±0.82	1.824	0.068
NT-proBNP, ng/mL	1,196.79±3,257.88	4,800.19±8,566.11	–7.11	<0.001
sST2, ng/mL	33.55±11.97	38.29±13.96	–5.23	<0.001
CHD type, n (%)			194.398	<0.001
Stable pectoris	679 (90.8)	201 (55.1)		
Unstable pectoris	51 (6.9)	95 (26.0)		
NSTEMI	8 (1.1)	24 (6.6)		
STEMI	10 (1.3)	45 (12.3)		
Comorbidity, n (%)				
Stroke	47 (6.3)	12 (3.3)	4.385	0.036
Hypertension	307 (41.0)	192 (52.6)	13.254	0.0003
Hyperlipidemia	384 (51.3)	219 (60.0)	7.416	0.007
Diabetes	113 (15.1)	89 (24.4)	14.377	0.0002
PAOD	19 (2.5)	21 (5.8)	7.310	0.007
Multivessel disease, n (%)	125 (16.7)	112 (30.7)	28.580	<0.001
Smoking history, n (%)			32.486	<0.001
None	427 (57.1)	143 (39.2)		
Current	96 (12.8)	75 (20.5)		
Past	225 (30.1)	147 (40.3)		
Treatment, n (%)				
ACEI	278 (37.2)	91 (24.9)	16.567	<0.001
Aspirin	714 (95.5)	328 (89.9)	12.842	<0.001
Clopidogrel	91 (12.2)	49 (13.4)	0.354	0.552
Statins	672 (89.8)	253 (69.3)	73.610	<0.001
Ticagrelor	12 (1.7)	7 (1.9)	0.144	0.705
Beta blockers	186 (24.9)	101 (27.7)	1.009	0.315

EF, ejection fraction; MACE, major adverse cardiovascular event; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; UA, uric acid; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; TC, total cholesterol; TG, triglyceride; NT-proBNP, N-terminal pro-brain natriuretic peptide; sST2, soluble ST2; CHD, coronary heart disease; NSTEMI, non-ST elevation acute myocardial infarction; STEMI, ST elevation acute myocardial infarction; PAOD, peripheral atherosclerosis obliterans disease; ACEI, angiotensin convert enzyme inhibitor.

Table 2 Multivariable Cox regression analysis

Items	HR	95% CI	P value
Age	1.019	1.009–1.029	<0.001
NT-proBNP	1.024	1.011–1.036	<0.001
SBP	0.992	0.987–0.997	0.003
sST2	1.010	1.001–1.018	0.025
TC	0.853	0.768–0.948	0.003
CABG	0.571	0.345–0.947	0.030
EF	1.016	1.002–1.030	0.025
Aspirin	0.652	0.449–0.946	0.024
UA	1.001	1.000–1.001	0.008
Fibrinogen	1.148	1.041–1.266	0.006
Hypertension	1.381	1.114–1.983	0.003

HR, hazard ratio; CI, confidence interval; NT-proBNP, N-terminal pro-brain natriuretic peptide; SBP, systolic blood pressure; sST2, soluble ST2; TC, total cholesterol; CABG, coronary artery bypass graft; EF, ejection fraction; UA, uric acid.

Global model fit

Likelihood ratio tests were carried out to evaluate the global fit of the models. The model that incorporated both sST2 and NT-proBNP had a better global fit than the models with only the established MACEs risk factors and NT-proBNP (P<0.001).

Discussion

NT-proBNP has been well recognized as an important predictor in CHD. However, for patients with CHD, the use of NT-proBNP for risk assessment is still controversial. Recent studies have shown sST2 to be a useful biomarker for stratifying risk in various clinical contexts. sST2 signals through a complex involving IL-33 (44,45). The activity of sST2 in heart-related conditions has yet to be fully established; however, in one study, the disruption of the ST2 gene in an experimental murine model suggested that it may be associated with conditions such as cardiac hypertrophy and fibrosis (46).

sST2 is involved in the activation of T-helper type 2 (Th2) cells and the expression of Th2-associated cytokines. Previous studies have reported an association between higher levels of sST2 in plasma and increased risk of mortality and nonfatal adverse cardiac events. In 2003, Weinberg *et al.* measured the serum levels of sST2 in

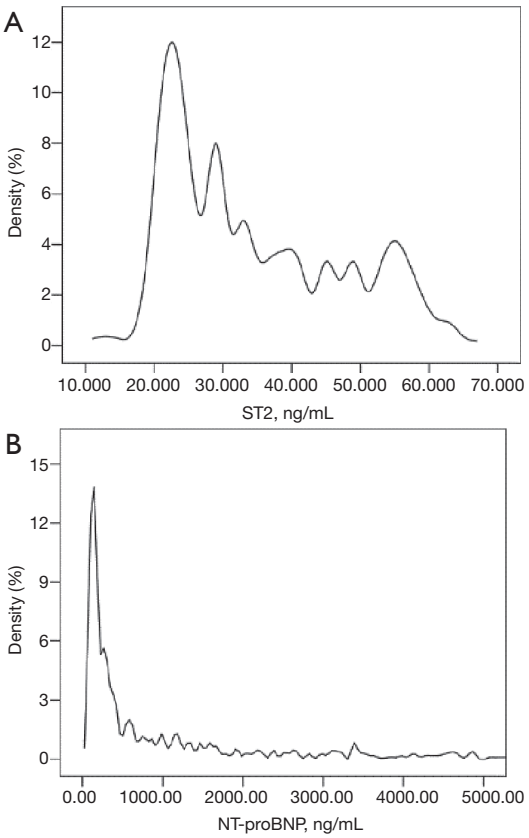

Figure 1 sST2 and NT-proBNP for predicting prognosis were identified by ROC curvilinear coordinates and the tangent coordinates. (A) Density plot for sST2 and (B) NT-proBNP. Values are expressed in ng/mL. sST2, soluble ST2; NT-proBNP, N-terminal pro-brain natriuretic peptide.

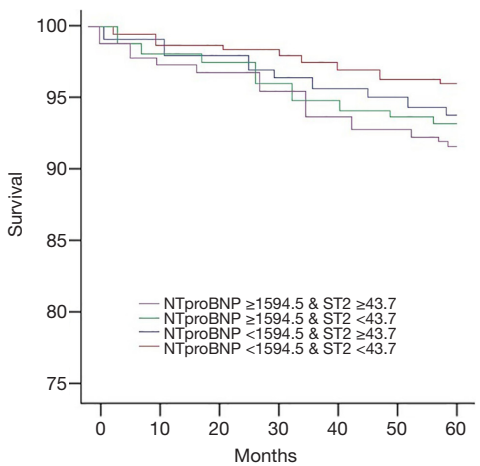

Figure 2 Kaplan-Meier survival curves according to sST2 and NT-proBNP levels (P<0.01). sST2, soluble ST2; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Table 3 C-statistics for Cox regression models predicting MACEs

MACE risk factors and biomarkers	C statistic for MACE	P value
MACE risk factors	0.742 (0.707–0.776)	<0.001
MACE risk factors plus NT-proBNP	0.756 (0.722–0.790)	<0.001
MACE risk factors plus ST2	0.745 (0.711–0.780)	<0.001
MACE risk factors plus NT-proBNP and ST2	0.758 (0.724–0.792)	<0.001

MACE, major adverse cardiovascular event; NT-proBNP, N-terminal pro-brain natriuretic peptide; SBP, systolic blood pressure; sST2, soluble ST2.

Table 4 Cohort characteristics according to ST tertile (25.76–39.39 ng/mL)

Items	Low tertile (n=371)	Medium tertile (n=371)	High tertile (n=371)	P value
Age, years	65 (55–73)	65 [56–74]	65 [56–75]	<0.001
SBP, mmHg	135 (120–150)	137 [122–152]	134 [120–149]	0.003
DBP, mmHg	74 (68–84)	74 [67–82]	73 [66–82]	0.953
EF, %	57 (52–61)	57 [51–60]	53 [44–59]	0.025
BMI, kg/m^2	25.0 (23.1–27.7)	25.0 (23.1–27.1)	25.2 (23.2–27.7)	0.797
Creatinine, μmol/L	78.4 (67.7–92.3)	77.7 (66.8–91.3)	81.0 (69.0–103.2)	0.918
UA, μmol/L	330.3 (270.1–404.8)	334.3 (269.8–390.7)	338.8 (273.7–429.7)	0.008
Glucose, mmol/L	5.84 (4.91–7.61)	6.08 (5.10–8.09)	6.48 (5.28–8.85)	0.458
HDL-C, mmol/L	1.06 (0.88–1.24)	1.01 (0.87–1.18)	1.03 (0.83–1.23)	0.799
LDL-C, mmol/L	2.18 (1.74–2.84)	2.28 (1.76–2.89)	2.26 (1.77–3.01)	0.794
GDF-15, pg/mL	2,158.82 (1,254.63– 3,463.96)	2,276.05 (1,401.49–3,806.81)	2,915.42 (1,617.45–5,245.61)	0.056
Fibrinogen, g/L	3.19 (2.74–3.80)	3.29 (2.80–4.03)	3.44 (2.82–4.27)	0.006
Co morbidity, n (%)				
Stroke	48 (12.9)	47 (12.7)	50 (13.5)	<0.001
Hypertension	259 (69.8)	266 (71.7)	255 (68.7)	0.050
Hyperlipidemia	109 (29.4)	102 (27.5)	76 (20.5)	0.001
Diabetes	113 (30.5)	130 (35.0)	138 (37.2)	0.007
PAOD	9 (2.4)	12 (3.2)	17 (4.6)	<0.001
TC, mmol/L	3.84 (3.24–4.59)	3.89 (3.31–4.65)	3.91 (3.30–4.72)	0.003
TG, mmol/L	1.28 (0.93–1.85)	1.33 (0.91–1.74)	1.20 (0.82–1.62)	0.470
CHD type, n (%)				
Stable pectoris	67 (18.1)	47 (12.7)	52 (14.0)	0.069
Unstable pectoris	258 (69.5)	284 (76.5)	231 (62.3)	0.103
NSTEMI	14 (3.8)	16 (4.3)	23 (6.2)	0.206
STEMI	32 (8.6)	24 (6.5)	64 (17.3)	0.094
Multivessel disease, n (%)	235 (63.3)	251 (67.7)	235 (63.3)	0.324

Table 4 *(continued)*

Table 4 *(continued)*

Items	Low tertile (n=371)	Medium tertile (n=371)	High tertile (n=371)	P value
Smoking history, n (%)				
None	210 (56.6)	210 (n=370, 56.7)	201 (54.2)	0.014
Current	69 (18.6)	65 (n=370, 17.6)	65 (17.5)	
Past	92 (24.8)	95 (n=370, 25.7)	105 (28.3)	
Treatments, n (%)				
ACEI	184 (n=370, 49.7)	176 (47.4)	185 (49.9)	0.544
Aspirin	346 (93.3)	342 (92.2)	325 (87.6)	0.024
CABG	23 (6.2)	35 (9.4)	21 (5.7)	0.030
Clopidogrel	313 (84.4)	306 (82.5)	312 (n=370, 84.3)	0.067
PCI	290 (78.2)	268 (72.2)	283 (76.3)	0.035
Statins	356 (n=370, 96.2)	349 (94.1)	333 (89.8)	<0.001
Ticagrelor	11 (n=370, 3.0)	6 (1.6)	6 (1.6)	0.291
Beta blocker	285 (n=370, 77.0)	271 (73.0)	269 (72.5)	0.031
Revascularization	22 (5.9)	22 (5.9)	29 (7.8)	<0.001
MACE, n (%)				
Primary outcome	77 (20.8)	84 (22.6)	140 (37.7)	<0.001
Cardiovascular death	26 (7.0)	28 (7.5)	59 (15.9)	<0.001
MI	6 (1.6)	12 (3.2)	12 (3.2)	<0.001
Stroke	14 (3.8)	16 (4.3)	19 (5.1)	<0.001
Noncardiovascular death	6 (1.6)	12 (3.2)	21 (5.7)	<0.001
PAD	4 (1.1)	1 (0.3)	1 (0.3)	0.566
HF	16 (4.3)	11 (3.0)	28 (7.5)	<0.001
NT-proBNP, ng/mL	279.4 (140.3–870.3)	330.6 (160.7–1,250.0)	790.6 (228.4–3,376.0)	<0.001
PAPPA, MoM	0.45 (0.39–0.53)	0.47 (0.40–0.55)	0.51 (0.42–0.63)	0.107

SBP, systolic blood pressure; DBP, diastolic blood pressure; EF, ejection fraction; BMI, body mass index; UA, uric acid; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; PAOD, peripheral atherosclerosis obliterans disease; TC, total cholesterol; TG, triglyceride; CHD, coronary heart disease; NSTEMI, non-ST elevation acute myocardial infarction; STEMI, ST elevation acute myocardial infarction; ACEI, angiotensin convert enzyme inhibitor; CABG, coronary artery bypass graft; MACE, major adverse cardiovascular event; MI, myocardial infarction; PAD, peripheral atherosclerosis disease; NT-proBNP, N-terminal pro-brain natriuretic peptide; HF, heart failure; PAPPA, Pregnancy-Associated Plasma protein-A.

Table 5 Cohort characteristics according to NT-proBNP Tertile (202.5–984.3 ng/mL)

Items	Low tertile (n=371)	Medium tertile (n=371)	High tertile (n=371)	P value
Age, years	62 [54–70]	65 [56–74]	70 [58–77]	<0.001
SBP, mmHg	137 [125–150]	135 [121–152]	132 [116–148]	0.003
DBP, mmHg	75 [69–83]	72 [66–81]	72 [66–81]	0.953
EF, %	59 [56–62]	56 [51–60]	48 [39–56]	0.025
BMI, kg/m^2	25.7 (23.7–27.9)	25.0 (23.4–27.3)	24.8 (22.4–27.0)	0.797
Creatinine, μmol/L	74.4 (65.6–85.4)	78.3 (67.6–89.8)	88.6(77.1–127.2)	0.918
UA, μmol/L	319.4 (263.4–376.3)	331.6 (267.6–389.9)	364.3 (284.2–461.6)	0.008
Glucose, mmol/L	5.81 (4.95–7.12)	5.93 (5.01–8.10)	6.68 (5.39–9.24)	0.458
HDL-C, mmol/L	1.05 (0.85–1.26)	1.05 (0.90–1.26)	0.98 (0.83–1.15)	0.799
LDL-C, mmol/L	2.21 (1.75–2.90)	2.21 (1.77–2.81)	2.31 (1.75–3.00)	0.794
GDF-15, pg/mL	2,020.12 (1,233.28–3,198.81)	2,245.64 (1,313.37–3,641.49)	3,438.36(1,907.20– 5,573.00)	0.056
Fibrinogen, g/L	3.10 (2.72–3.68)	3.28 (2.77–3.91)	3.60 (2.96–4.46)	0.006
Comorbidity, n (%)				
Stroke	40 (10.8)	52 (14.0)	53 (14.3)	0.001
Hypertension	257 (69.3)	253 (68.2)	270 (72.8)	0.050
Hyperlipidemia	133 (35.8)	86 (23.2)	68 (18.3)	0.001
Diabetes	99 (26.7)	125 (33.7)	157 (42.3)	0.007
PAOD	6 (1.6)	11 (3.0)	21 (5.7)	<0.001
TC, mmol/L	3.86 (3.28–4.67)	3.85 (3.31–4.49)	3.94 (3.24–4.70)	0.003
TG, mmol/L	1.30 (0.93–1.78)	1.24 (0.85–1.68)	1.27 (0.88–1.69)	0.470
CHD type, n (%)				
Stable pectoris	84 (22.6)	50 (13.5)	32 (8.6)	0.069
Unstable pectoris	265 (71.4)	261 (70.4)	247 (66.6)	0.103
NSTEMI	6 (1.6)	15 (4.0)	32 (8.6)	0.206
STEMI	16 (4.3)	45 (12.1)	59 (15.9)	0.094
Multivessel disease, n (%)	231 (62.3)	241 (65.0)	249 (67.1)	0.324
Smoking history, n (%)				
None	200 (53.9)	200 (53.9)	221(n=370, 59.7)	0.014
Current	63 (17.0)	75 (20.2)	61 (n=370, 16.5)	
Past	108 (29.1)	96 (25.9)	88 (n=370, 23.8)	
Treatments, n (%)				
ACEI	173 (46.6)	181 (48.8)	191(n=370, 51.6)	0.544
Aspirin	353 (95.1)	338 (91.1)	322 (86.8)	0.024
CABG	26 (7.0)	24 (6.5)	29 (7.8)	0.030
Clopidogrel	302(n=370,81.6)	316 (85.2)	313 (84.4)	0.067
PCI	280 (75.5)	294 (79.2)	267 (72.0)	0.035
Statins	357 (96.2)	348 (93.8)	333(n=370, 90.0)	<0.001

Table 5 *(continued)*

Table 5 *(continued)*

Items	Low tertile (n=371)	Medium tertile (n=371)	High tertile (n=371)	P value
Ticagrelor, n (%)	6 (1.6)	8 (2.2)	9 (n=370, 2.4)	0.291
Beta blockers	266 (71.7)	277 (74.7)	282 (76.2)	0.031
Revascularization	24 (6.5)	21 (5.7)	28 (7.5)	<0.001
MACE, n (%)				
Primary outcome	55 (14.8)	76 (20.5)	170 (45.8)	
Cardiovascular death	13 (3.5)	16 (4.3)	84 (22.6)	<0.001
MI	5 (1.3)	11 (3.0)	14 (3.8)	<0.001
Stroke	13 (3.5)	11 (3.0)	25 (6.7)	<0.001
Noncardiovascular death	5 (1.3)	13 (3.5)	21 (5.7)	<0.001
PAD	2 (0.5)	4 (1.1)	0 (0.0)	0.566
HF	3 (0.8)	15 (4.0)	37 (10.0)	<0.001
ST2, median (IQR), ng/mL	28.19 (22.61–38.29)	30.16 (23.84–42.16)	37.60 (26.06–51.45)	0.025
PAPPA, median (IQR), MoM	0.45 (0.38–0.51)	0.46 (0.40–0.55)	0.52 (0.43–0.62)	0.107

SBP, systolic blood pressure; DBP, diastolic blood pressure; EF, ejection fraction; BMI, body mass index; UA, uric acid; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; PAOD, peripheral atherosclerosis obliterans disease; TC, total cholesterol; TG, triglyceride; CHD, coronary heart disease; NSTEMI, non-ST elevation acute myocardial infarction; STEMI, ST elevation acute myocardial infarction; ACEI, angiotensin convert enzyme inhibitor; CABG, coronary artery bypass graft; MACE, major adverse cardiovascular event; MI, myocardial infarction; PAD, peripheral atherosclerosis disease; HF, heart failure; NT-proBNP, N-terminal pro-brain natriuretic peptide; IQR, interquartile range; PAPPA, Pregnancy-Associated Plasma protein-A.

Table 6 Reclassification of patients with CHD with MACE or without MACE using NT-proBNP + ST2

Models with risk factors	Model with MACE risk factors + NT-proBNP + ST2			
	Low tertile (<15%)	Medium tertile (15–28%)	High tertile (>28%)	Total no.
Patients with MACE				
Low tertile (<15%)	46	6	4	56
Medium tertile (15–28%)	13	62	22	97
High tertile (>28%)	3	15	194	212
Total No.	62	83	220	365
Patients without MACE				
Low tertile (<15%)	266	18	0	284
Medium tertile (15–28%)	48	218	16	282
High tertile (>28%)	0	39	143	182
Total No.	314	275	159	748

CHD, coronary heart disease; MACE, major adverse cardiovascular event; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Table 7 Reclassification of patients with CHD with MACE or without MACE using ST2

Models with factors + NT-proBNP	Model with MACEs risk factors + NT-proBNP + ST2			
	Low tertile (<15%)	Medium tertile (15–28%)	High tertile (>28%)	Total no.
Patients with MACEs				
Low tertile (<15%)	42	8	1	51
Medium tertile (15–28%)	20	60	19	99
High tertile (>28%)	0	15	200	215
Total No.	62	83	220	365
Patients without MACEs				
Low tertile (<15%)	282	21	0	303
Medium tertile (15–28%)	32	244	4	280
High tertile (>28%)	0	10	155	165
Total No.	314	275	159	748

CHD, coronary heart disease; MACE, major adverse cardiovascular event; NT-proBNP, N-terminal pro-brain natriuretic peptide.

patients with chronic nonischemic HF upon admission and at 2 weeks after admission, and found that changes in sST2 level could predict poor prognosis of chronic heart failure (CHF) (3). Dieplinger *et al.* demonstrated that for patients with stable coronary artery disease (CAD), a higher level of sST2 could independently predict mortality of all causes over the long term and offer complementary prognostic value to hs-cTnT and NT-proBNP (44). Furthermore, in the Multi-Ethnic Study of Atherosclerosis (MESA), the investigators found that NT-proBNP surpassed other clinical risk factors as an independent predictor for incident CAD and cardiovascular disease (CVD). The Dallas Heart Study investigated a low-risk population, and it revealed that sST2 was associated with increased all-cause and cardiovascular mortality (46).

For patients with acute HF, sST2 is a powerful and reliable prognostic predictor (47). Meanwhile, for patients with CHD, it has also been shown that sST2 is an independent and complementary risk factor along with NT-proBNP (48). sST2 also served as an effective marker for the identification of CHD patients carrying risk of sudden cardiac death in a nested case-control study (49). In the current study, high-sensitivity sST2 provided independent prognostic information for predicting the occurrence of MACEs from all causes over the other variables studied before, including NT-proBNP. Thus, this study has unearthed new data regarding the value of sST2 in predicting the prognosis of CHD, as well as the complementary roles of both sST2 and NT-proBNP.

This method was evaluated by Ky in a younger, healthier group of subjects (50). The combined assessment of sST2 and NT-proBNP was discovered to moderately improve risk stratification within the group. Nevertheless, there was no significant improvement when sST2 was incorporated into a clinical model with NT-proBNP. Risk evaluation can be affected by differences in patient characteristics, such as age or disease severity. Furthermore, the length of follow-up in our study differed to those in previous analyses, which may offer another explanation for the differences observed between the studies. Meanwhile, the area under the curve (AUC) was 0.81 in Ky *et al.*'s study, compared with 0.742 in the current analysis (50).

This study analyzed the data from a group of CHD patients and incorporated sST2 (reflective of myocardial fibrosis and remodeling) and NT-proBNP (indicative of myocardial stretch) into a model with established risk factors of MACE, which led to an improvement in the risk stratification for death. When the model's discrimination and reclassification abilities, calibration, and global fit were evaluated, it maintained a powerful ability to assess the risk of MACE occurrence among patients in the cohort.

Nevertheless, this study has some limitations. The levels of sST2 and NT-proBNP of the patients were measured based on frozen blood samples rather than fresh samples, which could have possibly influenced the absolute levels of the biomarkers. However, there is evidence to suggest that NT-proBNP and ST2 are not significantly affected by freeze-thaw cycles (51).

Although MACEs risk factors have been modified (52-54), at present there is only limited evidence to indicate that the risk of MACE can be reduced by lowering the levels of sST2 and NT-proBNP. Data for NT-proBNP from pilot studies and randomized clinical trials show that targeted therapy to reduce NT-proBNP levels may pave the way for the more effective use of proven CHD therapies, thus improving clinical outcomes (55,56). sST2 offers promise as a prognostic marker in the management of cardiovascular diseases. It can be used in combination with NT-proBNP to guide the treatment of cardiovascular diseases and help to reduce adverse clinical outcomes.

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Footnote

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