Published in final edited form as:

Biomarkers. 2019 May ; 24(3): 268–276. doi:10.1080/1354750X.2018.1556338.

sST2 as a Novel Biomarker for the Prediction of In-hospital Mortality after Coronary Artery Bypass Grafting

Meagan E. Stabler, PhD, CHES^{a,b,*}, Michael E. Rezaee, MD, MPH^c, Devin M. Parker, MS^a, Todd A. MacKenzie, PhD, MSc^{a,d,e}, Andrew R. Bohm, MS^a, Anthony W. DiScipio, MD^f, David J. Malenka, MD^{a,d,g}, and Jeremiah R. Brown, PhD, MS^{a,b,e}

^aThe Dartmouth Institute for Health Policy & Clinical Practice, Dartmouth Geisel School of Medicine, Lebanon, NH, USA;

^bDepartment of Epidemiology, Dartmouth Geisel School of Medicine, Lebanon, NH, USA;

^cSection of Urology, Department of Surgery, Dartmouth Hitchcock Medical Center, Lebanon, NH, USA;

^dDepartment of Medicine, Dartmouth Geisel School of Medicine, Lebanon, NH, USA;

^eDepartment of Biomedical Data Science, Dartmouth Geisel School of Medicine, Lebanon, NH, USA;

^fDepartment of Surgery, Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA;

^gDepartment of Community and Family Medicine, Dartmouth Geisel School of Medicine, Lebanon, NH, USA;

Abstract

Objectives—Soluble suppression of tumorigenicity 2 (sST2) biomarker is an emerging predictor of adverse clinical outcomes, but its prognostic value for in-hospital mortality after coronary artery bypass grafting (CABG) is not well understood. This study measured the association between operative sST2 levels and in-hospital mortality after CABG.

Methods—A prospective cohort of 1,560 CABG patients were analysed from the Northern New England Cardiovascular Disease Study Group Biomarker Study. The primary outcome was in-hospital mortality after CABG surgery (n=32).

Results—After risk adjustment, patients in the third tercile of pre-, post- and pre-to-postoperative sST2 values experienced significantly greater odds of in-hospital death compared to patients in the first tercile of sST2 values. The addition of both postoperative and pre-to-postoperative sST2 biomarker significantly improved ability to predict in-hospital mortality status following CABG surgery, compared to using the EuroSCORE II mortality model alone, (c-statistic: 0.83 [95% CI:

*Corresponding author: Meagan E. Stabler, PhD, CHES, 1 Medical Center Drive, Dartmouth-Hitchcock Medical Center, Lebanon, NH 03756; Ph: 603-653-3597; Fax: 603-653-3554; Meagan.E.Stabler@dartmouth.edu.

Data availability statement: The data that support the findings of this study are available from the Northern New England Cardiovascular Disease Study Group Biomarker Study. Restrictions apply to the availability of these data, which were used under licence for this study. Data are available with permission from of the Northern New England Cardiovascular Disease Study Group and IRB approval.

0.75, 0.92], p-value 0.0213) and (c-statistic: 0.83 [95% CI: 0.75, 0.92], p-value 0.0215), respectively.

Conclusion—sST2 values are associated with in-hospital mortality after CABG surgery and postoperative and pre-to-post operative sST2 values improve prediction. Our findings suggest that sST2 can be used as a biomarker to identify adult patients at greatest risk of in-hospital death after CABG surgery.

Keywords

Cardiovascular surgery; CABG; biomarker; sST2; prediction; in-hospital mortality

Introduction

In-hospital mortality rates for cardiac surgery patients range from 3% to 5%, with a principal cause of death being cardiac in nature more than 60% of the time (Pearse *et al.*, 2012, Mazzeffi *et al.*, 2014, Paparella *et al.*, 2014, Litwinowicz *et al.*, 2015). Identifying patients at the greatest risk of in-hospital death after cardiac surgery remains of significant interest to clinicians, researchers, patients and families. Cardiac biomarkers may serve as important tools in successfully identifying these patients.

Soluble suppression of tumorigenicity 2 (sST2), a member of the interleukin (IL)-1 family, is regarded as a promising biomarker recently identified for cardiac disease. sST2 elevation has been shown to be associated with heart failure and death with patients in the highest quartile of sST2 levels having over 3 times increased risk for either outcome when compared to those in the lowest quartile (Shah and Januzzi, 2010, Braunwald, 2013). sST2 is up regulated by cardiac myocytes in response to mechanical overload and is known to result in hypertrophic and fibrotic changes to the myocardium (Januzzi, 2013, Richards *et al.*, 2015). Research has demonstrated that sST2 is associated with heart failure severity and that it is an independent predictor of mortality among heart failure patients (Ky *et al.*, 2011). When used in conjunction with Troponin T and N-terminal prohormone of brain natriuretic peptide (NT-proBNP), sST2 is additive for risk prediction (Pascual-Figal *et al.*, 2011). Additionally, sST2 is an independent predictor of cardiovascular death and heart failure in ST-elevation myocardial infarction (STEMI) patients and is prognostic for the onset of heart failure, cardiovascular disease, and death in seemingly healthy adults (Shimpo *et al.*, 2004, Wang *et al.*, 2012).

Despite sST2's demonstrated prognostic utility in the heart failure and acute coronary syndrome populations, sST2 as a biomarker for in-hospital mortality after coronary artery bypass grafting (CABG) surgery has not been well studied (Aldous *et al.*, 2012, Marino *et al.*, 2017). The few studies that have assessed preoperative sST2 in predicting mortality after aortic valve replacement surgery assessed the endpoint at one-year after surgery rather than in-hospital mortality (Lindman *et al.*, 2015, Schmid *et al.*, 2017, Stundl *et al.*, 2017, Wernly *et al.*, 2017). Therefore, we undertook this study to determine the association between pre- and postoperative sST2 values and in-hospital mortality after CABG surgery.

Materials and Methods

Northern New England Cardiovascular Disease Study Group (NNE) Biomarker Study

This study used data and blood specimens stored from the Northern New England Cardiovascular Disease Study Group (NNE) Biomarker Study, a regional consortium of eight medical centres in northern New England with experience in risk prediction in CABG surgery, to conduct a prospective cohort analysis. Patients undergoing CABG surgery at any of the eight hospitals participating in the NNE Biomarker Study from 2004 to 2007 (N=1,690) were included. Patients were excluded if their preoperative blood was not banked (n=130), leaving 1,560 patients included in the preoperative analysis. When analysing postoperative levels of sST2 and the change in levels from preoperative to postoperative, patients without pre- or postoperative blood banked were excluded (n=517), leaving 1,173 patients included in the postoperative analysis. Of the 517 patients who were excluded for missing postoperative sST2 measurement, 12 died in the hospital before postoperative measurement occurred. The Committee for the Protection of Human Subjects at Dartmouth College approved this study for the prospective cohort with patient consent.

The Northern New England (NNE) Biomarker Study was comprised of patient data contributed by any of eight hospitals located in New Hampshire, Maine and Vermont belonging to the Northern New England Cardiovascular Disease Study Group (NNECDSG) (Brown *et al.*, 2010). The NNECDSG is a voluntary, regional collaborative of clinicians, research scientists, and hospital administrators dedicated to improving the quality, safety, and effectiveness of care delivered to patients undergoing coronary revascularization and open-heart surgery. All hospitals in this consortium submit data on cases with validation of procedure numbers and mortality conducted every two years. Registry data includes patient characteristics, procedural indication, clinical variables and in-hospital outcomes. All institutional review boards for each contributing hospital reviewed and approved the data collection for the NNECDSG as well as the conduct of this study.

Primary Endpoint

The primary endpoint of this study was in-hospital mortality after CABG surgery.

Primary Exposure

Preoperative, postoperative and the difference between pre- and post-operative (i.e. pre-to-post) sST2 values served as the main exposures for this study. Blood samples were preoperatively collected prior to incision at each participating site in a 10-mL serum tube from 2003–2007. Biomarker measurement was postoperatively collected on the first day after CABG surgery. Blood clotted at room temperature for 20 minutes to separate out the red blood cells, the tubes were centrifuged at 3500 rpm for 20 minutes, and the sera stored at the respective medical centres below –80 degrees Celsius until transportation on dry ice to the Laboratory for Clinical and Biomedical Research in Colchester, Vermont where they were stored at –80 degrees Celsius until measurement. Frozen serum was analysed at a central laboratory, at the same time for biomarker measurement. Markers were measured by Roche Diagnostics Elecsys 2010. Adjusted sST2 values were calculated to correct for a reagent shift in the assays used to measure sST2. For use in all analyses, sST2 values were

categorized into terciles, as the normal range of sST2 among cardiac surgery patients has not yet been established. The preoperative and postoperative sST2 cut-off values are represented in Table 1.

Statistical Analysis

Descriptive statistics were used to examine patient and procedural characteristics as well as in-hospital mortality across sST2 terciles. Univariate and multivariate logistic regression was used to examine the relationship between sST2 terciles and in-hospital mortality. Adjustment was carried out using a European System for Cardiac Operative Risk Evaluation (EuroSCORE) II mortality model, which includes age, sex, chronic obstructive pulmonary disease (COPD), poor mobility secondary to musculoskeletal or neurological dysfunction, previous cardiac surgery, serum creatinine >200 µmol/L, critical preoperative state, unstable angina, left ventricle (LV) dysfunction moderate or LV ejection fraction 30–50%, LV dysfunction poor or LV ejection fraction <30, myocardial infarction 7 days or less days before CABG, pulmonary hypertension, priority (emergency or emergent salvage, urgent, non-urgent), and other isolated CABG surgery (Nashef *et al.*, 2012). After harmonizing NNE variables to the EuroSCORE II, three variables were not available including extracardiac arteriopathy, active endocarditis, and postinfarct septal rupture. Surgery on thoracic aorta was not included in the model because of the study population includes patients who have undergone CABG surgery. One of the most widely used risk index for cardiac surgery, the EuroSCORE II validated model was specifically developed to predict the risk of death after a heart operation via logistic regression with patient, cardiac, and operation risk factors (Nashef *et al.*, 2012, Noyez *et al.*, 2012).

Missing values were addressed via the Shahian and colleagues replacement approach, which replaced missing values of indicator variables with zero, categorical variables with the most common category and continuous variables with conditional medians (Shahian and Grover, 2014). Covariate missingness ranged from 0.0% to 5.0% in the full sample (i.e. n=1,560 patients). All analyses were conducted using Stata 13.1 (College Station, TX).

Results

Patient and procedural characteristics can be viewed in Table 2. Overall, 92.3% (n=1,560) of the patients enrolled in the NNE Biomarkers Study met inclusion criteria for the preoperative analysis. Global in-hospital mortality for the study cohort was 32 (2.1%). The average age of the final cohort was 65.3 years, 23.7% were female, 37.2% were diabetic, and 13.0% had COPD. Patients with a presence of a higher AKIN (Acute Kidney Injury Network) stage, preoperative intra-operative balloon pump, unstable angina, COPD, prior CABG, and those who have received transfused blood had a significantly higher likelihood of experiencing in-hospital mortality. Increased age, body surface area, and female gender were also associated with in-hospital death.

Patients in the highest preoperative sST2 tercile were more severely ill than patients in the first or second sST2 tercile (not shown in Table 2). These patients had a significantly higher likelihood of being older, diabetic, male or a smoker. Additionally, they were more likely to have reduced ejection fraction, congestive heart failure, prior myocardial infarction or any

vascular disease, and higher preoperative creatinine measurements. Patients in the third tercile were also more likely to be in a higher AKIN stage, higher priority class, and need an intra-operative balloon pump and packed red blood cell transfusion. As expected, patients in the third sST2 tercile had a higher occurrence of in-hospital mortality. The relationship between sST2 terciles and in-hospital mortality, with patient and procedural risk factor adjustment, are presented in the following sections. Receiver operating characteristic (ROC) curves are also included to show the added predictive value of sST2 levels compared to the clinical model alone.

Preoperative sST2

Patient outcomes by terciles of preoperative sST2 values are presented in Table 3. Patients with higher preoperative sST2 values were at greater risk of in-hospital mortality ($p=0.006$), renal failure ($p=0.021$), mediastinitis ($p=0.024$), stroke ($p=0.007$), low cardiac output ($p=0.021$) and pneumonia ($p=0.027$).

Results from the crude and adjusted logistic regression analysis between preoperative sST2 and in-hospital mortality can be seen in Table 4. Compared to the first preoperative sST2 tercile, the unadjusted odds of in-hospital mortality for CABG patients in the third preoperative sST2 tercile was 3.86 (95% CI: 1.43 – 10.42; $p=0.008$). After adjustment for patient, cardiac and operation risk factors the association remained, with patients in the third preoperative sST2 tercile having 3.86 times the odds of experiencing in-hospital mortality (95% CI: 1.43 – 10.46; $p=0.008$) compared to those in the first tercile. The area under the ROC curve for the EuroSCORE II mortality risk model was 0.71 (95% CI: 0.62, 0.80) for the preoperative $n=1,560$ sample. The predictive power of the model remained constant when including preoperative sST2 with the EuroSCORE II model (c-statistic: 0.71 (95% CI: 0.61, 0.80), p -value: 0.9652).

Postoperative sST2

Similarly, patients with higher postoperative sST2 values experienced increased in-hospital mortality, atrial fibrillation, renal failure, low cardiac output, pneumonia and leg wound infection (Table 5). Compared to the first tercile of postoperative sST2 values, the unadjusted odds of in-hospital mortality in the third tercile were 8.57 (95% CI: 1.97 – 37.34; $p=0.004$). After adjusting with the EuroSCORE II risk factors, the predictive power of postoperative sST2 decreased for patients in the third sST2 tercile having 7.87 times the odds of experiencing in-hospital mortality (95% CI: 1.80 – 34.54; $p=0.006$) compared to those in the first tercile. The area under the ROC curve for the EuroSCORE II was 0.74 (95% CI: 0.63, 0.84) for the postoperative $n=1,173$ sample. The mortality model with postoperative sST2 biomarker significantly improved discrimination between patients in-hospital mortality status following CABG surgery (c-statistic: 0.83 (95% CI: 0.75, 0.92), p -value 0.00213).

Difference between Pre- and Postoperative sST2

Patients in the third tercile had 8.8 times the odds of in-hospital mortality compared to the first tercile (95% CI: 2.0–38.3). After adjustment, the odds of in-hospital mortality among patients in the third tercile were 8.1 (95% CI: 1.85–35.51; $p=0.006$) when compared to the

first tercile (Table 4). The area under the ROC curve for the EuroSCORE II mortality risk model was 0.74 (95% CI: 0.63, 0.84) for the pre-to-postoperative sST2. The mortality model with pre-to-postoperative sST2 biomarker significantly improved discrimination between patients in-hospital mortality status following CABG surgery (c-statistic: 0.83 (95% CI: 0.75, 0.92), p-value 0.0215).

Discussion

We are the first to show a relationship between the biomarker sST2 and in-hospital mortality among patients undergoing CABG surgery. After adjustment, we found that patients in the third tercile of pre-, post-, and pre-to-postoperative sST2 values had significantly higher odds of in-hospital death compared to patients in the first tercile of the respective sST2 values (Figure 5). Postoperative and pre-to-post operative sST2 values improved prediction of in-hospital mortality after CABG surgery, compared to using a clinical mortality risk model alone. Our findings indicate that operative sST2 values are associated with in-hospital mortality and that sST2 may be used as a tool to identify patients at the highest risk death.

sST2 is a member of the interleukin-1 receptor family which is used as a clinical biomarker for mechanical cardiac stress (Shah and Januzzi, 2010). Current research suggests that when the myocardium stretches, sST2 is upregulated, causing the level of soluble sST2 in the blood to rise rapidly, often in conjunction with NT-proBNP (Braunwald, 2013). Specifically, sST2 is believed to be a factor in the immunologic process by working in conjunction with T helper 2 mediated responses for cardiac remodelling (Coyle *et al.*, 1999). Increased sST2 levels have been shown to be independently associated with increases in hemodynamic decompensation, and cardiac inflammation and infarction (Shah and Januzzi, 2010). In regards to clinical outcomes, sST2 elevation has been shown to be indicative of heart failure and death with patients in the highest quartile of sST2 levels having an over 3 times increased risk for either outcome when compared to those in the lowest quartile (Shah and Januzzi, 2010, Braunwald, 2013).

Soluble ST2 is a novel biomarker of cardiovascular stress that has been associated with cardiovascular disease and heart failure. Research from the Framingham Offspring Study observed a direct relation between elevated sST2 levels and greater aortic stiffness, putting patients at increased risk of myocardial infarction, stroke and death (Andersson *et al.*, 2016). Higher sST2 levels have also been demonstrated to be a significant predictor of incident hypertension (Ho *et al.*, 2013b). While recent studies have shown an association with elevated sST2 levels and chronic kidney disease development, a community-based multicentre cohort of older adults without heart failure showed no association between higher sST2 and risk of incident chronic kidney injury (Bansal *et al.*, 2016). Similarly, among patients in the Framingham Offspring Study, no association was noted between higher sST2 and kidney function decline (Ho *et al.*, 2013a).

sST2 has been shown to add prognostic utility for predicting 90-day all-cause mortality in a heterogeneous cohort of patients admitted to the intensive care unit (Dieplinger *et al.*, 2016). Investigators used a multimarker approach with the routinely used severity score (Simplified Acute Physiology Score (SAPS) II), interleukin 6 (IL-6) and sST2 at baseline to identify

patients at low, intermediate and high risks for all-cause mortality in critically ill patients. Patients with increased values of sST2 values greater than 103 ng/mL had the poorest outcomes (Dieplinger *et al.*, 2016).

We uniquely utilized terciles to categorize sST2 values in our study, as normal values of sST2 after cardiac surgery are currently unknown. Willems and colleagues demonstrated that sST2 values increase significantly after cardiac surgery, however this increase differs by the type of cardiac surgery performed and by the time in which the sample is collected (Willems *et al.*, 2013). Therefore, determining at what time sST2 measurement has the highest prognostic value for cardiac surgery patients is necessary especially when using the pre-to-post sST2 levels for their predictive value.

Both baseline sST2 levels at admission and the change in sST2 over a hospital course have shown to be independent predictors of mortality in heart failure (Boisot *et al.*, 2008, Januzzi, 2013). Our study demonstrated that preoperative, postoperative and the difference in pre- and postoperative sST2 levels were significantly associated with in-hospital mortality. Our findings are similar to previous research which shows the importance of preoperative sST2 levels in the prediction of one-year mortality after aortic valve implantation. (Schmid *et al.*, 2017, Stundl *et al.*, 2017, Wernly *et al.*, 2017) In addition, the current study highlights the clinical value of obtaining postoperative sST2 values in efforts to decrease in-hospital mortality after CABG surgery. Postoperative sST2 values could be indicative of clinical or injury-related risk factors during the surgery itself, which could provide a unique opportunity for public health interventions.

Understanding normal values of sST2 compared to a pathologic condition is necessary when determining the clinical usefulness of this biomarker. In addition to establishing the normal range of sST2 among cardiac surgery patients, future research should quantify timestamped changes in sST2 levels throughout the operative period to determine the best time to harvest a blood sample. A correlation study comparing the prognostic value between sST2 and, a currently available biomarker, NT proBNP is also warranted. This comparison could highlight advantages of sST2 as a novel biomarker.

Strengths/Limitations

This was a large, multicentre, regional study that leveraged data from multiple hospitals, which supports the generalizability of our results. Additionally, the NNE registry is both comprehensive and extensive in terms of the patient and procedural data that it contains. The completeness of this data ensures that adequate risk adjustment was carried out in line with The Society of Thoracic Surgeons recommendations.

Research has demonstrated that sST2 is additive to the prognostic value of BNP in heart failure patients. We did not include or control for BNP values in our study, which may have resulted in overestimation of the relationship between sST2 and in-hospital mortality. We did not include BNP because only 10.6% of our sample had heart failure and sST2 has been proven to be an independent predictor of mortality in multiple patient populations regardless of BNP. In addition, our findings may not be as applicable to females, as they only represented 23.7% of the patients include in this study. Lastly, with a primary outcome of in-

hospital mortality, we were unable to assess the relationship between sST2 and mortality at increased lengths of follow-up.

Conclusions

We report that sST2 is significantly associated with in-hospital mortality among CABG patients. This relationship was uniquely assessed with terciles of sST2 values measured at different time points during the operative period. Postoperative and pre-to-post operative sST2 values improved prediction of in-hospital mortality after CABG surgery, compared to using a clinical mortality risk model alone. Our findings suggest that sST2 can be used as a biomarker to identify adult patients at greatest risk of in-hospital death after CABG surgery.

Acknowledgments:

None

Funding Statement: This research is supported by the National Heart Lung and Blood Institute R01HL119664 (PI: Brown). All authors are research staff or investigators on the grant.

Declaration of Interest: The authors report no conflict of interest. This research is supported by the National Heart Lung and Blood Institute R01HL119664 (PI: Brown). All authors are research staff or investigators on the grant.

References

- Aldous SJ, Richards AM, Troughton R & Than M, 2012 ST2 has diagnostic and prognostic utility for all-cause mortality and heart failure in patients presenting to the emergency department with chest pain. *J Card Fail*, 18, 304–10. [PubMed: 22464771]
- Andersson C, Enserro D, Sullivan L, Wang TJ, Januzzi JL Jr., Benjamin EJ, Vita JA, Hamburg NM, Larson MG, Mitchell GF & Vasan RS, 2016 Relations of circulating GDF-15, soluble ST2, and troponin-I concentrations with vascular function in the community: The Framingham Heart Study. *Atherosclerosis*, 248, 245–51. [PubMed: 26972631]
- Bansal N, Katz R, Seliger S, Defilippi C, Sarnak MJ, Delaney JA, Christenson R, De Boer IH, Kestenbaum B, Robinson-Cohen C, Ix JH & Shlipak MG, 2016 Galectin-3 and Soluble ST2 and Kidney Function Decline in Older Adults: The Cardiovascular Health Study (CHS). *Am J Kidney Dis*, 67, 994–6. [PubMed: 26830253]
- Boisot S, Beede J, Isakson S, Chiu A, Clopton P, Januzzi J, Maisel AS & Fitzgerald RL, 2008 Serial sampling of ST2 predicts 90-day mortality following destabilized heart failure. *J Card Fail*, 14, 732–8. [PubMed: 18995177]
- Braunwald E, 2013 Heart failure. *JACC Heart Fail*, 1, 1–20. [PubMed: 24621794]
- Brown JR, Mackenzie TA, Dacey LJ, Leavitt BJ, Braxton JH, Westbrook BM, Helm RE, Klemperer JD, Frumiento C, Sardella GL, Ross CS & O’connor GT, 2010 Using biomarkers to improve the preoperative prediction of death in coronary artery bypass graft patients. *J Extra Corpor Technol*, 42, 293–300. [PubMed: 21313927]
- Coyle AJ, Lloyd C, Tian J, Nguyen T, Eriksson C, Wang L, Ottoson P, Persson P, Delaney T, Lehar S, Lin S, Poisson L, Meisel C, Kamradt T, Bjerke T, Levinson D & Gutierrez-Ramos JC, 1999 Crucial role of the interleukin 1 receptor family member T1/ST2 in T helper cell type 2-mediated lung mucosal immune responses. *J Exp Med*, 190, 895–902. [PubMed: 10510079]
- Dieplinger B, Egger M, Leitner I, Firlinger F, Poelz W, Lenz K, Haltmayer M & Mueller T, 2016 Interleukin 6, galectin 3, growth differentiation factor 15, and soluble ST2 for mortality prediction in critically ill patients. *J Crit Care*, 34, 38–45. [PubMed: 27288608]
- Ho JE, Hwang SJ, Wollert KC, Larson MG, Cheng S, Kempf T, Vasan RS, Januzzi JL, Wang TJ & Fox CS, 2013a Biomarkers of cardiovascular stress and incident chronic kidney disease. *Clin Chem*, 59, 1613–20. [PubMed: 23873716]

- Ho JE, Larson MG, Ghorbani A, Cheng S, Vasan RS, Wang TJ & Januzzi JL Jr., 2013b Soluble ST2 predicts elevated SBP in the community. *J Hypertens*, 31, 1431–6; discussion 1436. [PubMed: 23615326]
- Januzzi JL Jr., 2013 ST2 as a cardiovascular risk biomarker: from the bench to the bedside. *J Cardiovasc Transl Res*, 6, 493–500. [PubMed: 23558647]
- Ky B, French B, McCloskey K, Rame JE, McIntosh E, Shahi P, Dries DL, Tang WH, Wu AH, Fang JC, Boxer R, Sweitzer NK, Levy WC, Goldberg LR, Jessup M & Cappola TP, 2011 High-sensitivity ST2 for prediction of adverse outcomes in chronic heart failure. *Circ Heart Fail*, 4, 180–7. [PubMed: 21178018]
- Lindman BR, Breyley JG, Schilling JD, Vatterott AM, Zajarias A, Maniar HS, Damiano RJ Jr., Moon MR, Lawton JS, Gage BF, Sintek MA, Aquino A, Holley CL, Patel NM, Lawler C, Lasala JM & Novak E, 2015 Prognostic utility of novel biomarkers of cardiovascular stress in patients with aortic stenosis undergoing valve replacement. *Heart*, 101, 1382–8. [PubMed: 26037104]
- Litwinowicz R, Bartus K, Drwila R, Kapelak B, Konstanty-Kalandyck J, Sobczynski R, Wierzbicki K, Bartus M, Chrapusta A, Timek T, Bartus S, Oles K & Sadowski J, 2015 In-hospital mortality in cardiac surgery patients after readmission to the intensive care unit: a single-center experience with 10,992 patients. *J Cardiothorac Vasc Anesth*, 29, 570–5. [PubMed: 26009285]
- Marino R, Magrini L, Orsini F, Russo V, Cardelli P, Salerno G, Hur M & Di Somma S, 2017 Comparison Between Soluble ST2 and High-Sensitivity Troponin I in Predicting Short-Term Mortality for Patients Presenting to the Emergency Department With Chest Pain. *Ann Lab Med*, 37, 137–146. [PubMed: 28029000]
- Mazzeffi M, Zivot J, Buchman T & Halkos M, 2014 In-hospital mortality after cardiac surgery: patient characteristics, timing, and association with postoperative length of intensive care unit and hospital stay. *Ann Thorac Surg*, 97, 1220–5. [PubMed: 24360878]
- Nashef SA, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR & Lockowandt U, 2012 EuroSCORE II. *Eur J Cardiothorac Surg*, 41, 734–44; discussion 744–5. [PubMed: 22378855]
- Noyez L, Kievit PC, Van Swieten HA & De Boer MJ, 2012 Cardiac operative risk evaluation: The EuroSCORE II, does it make a real difference? *Neth Heart J*, 20, 494–8. [PubMed: 23055057]
- Paparella D, Guida P, Di Eusanio G, Caparrotti S, Gregorini R, Cassese M, Fanelli V, Speziale G, Mazzei V, Zaccaria S, Schinosa Lde L & Fiore T, 2014 Risk stratification for in-hospital mortality after cardiac surgery: external validation of EuroSCORE II in a prospective regional registry. *Eur J Cardiothorac Surg*, 46, 840–8. [PubMed: 24482382]
- Pascual-Figal DA, Manzano-Fernandez S, Boronat M, Casas T, Garrido IP, Bonaque JC, Pastor-Perez F, Valdes M & Januzzi JL, 2011 Soluble ST2, high-sensitivity troponin T- and N-terminal pro-B-type natriuretic peptide: complementary role for risk stratification in acutely decompensated heart failure. *Eur J Heart Fail*, 13, 718–25. [PubMed: 21551163]
- Pearse RM, Moreno RP, Bauer P, Pelosi P, Metnitz P, Spies C, Vallet B, Vincent JL, Hoeft A & Rhodes A, 2012 Mortality after surgery in Europe: a 7 day cohort study. *Lancet*, 380, 1059–65. [PubMed: 22998715]
- Richards AM, Di Somma S & Mueller T, 2015 ST2 in stable and unstable ischemic heart diseases. *Am J Cardiol*, 115, 48b–58b.
- Schmid J, Stojakovic T, Zweiker D, Scharnagl H, Maderthaner RD, Scherr D, Maier R, Schmidt A, Marz W, Binder JS & Rainer PP, 2017 ST2 predicts survival in patients undergoing transcatheter aortic valve implantation. *Int J Cardiol*, 244, 87–92. [PubMed: 28651919]
- Shah RV & Januzzi JL Jr., 2010 ST2: a novel remodeling biomarker in acute and chronic heart failure. *Curr Heart Fail Rep*, 7, 9–14. [PubMed: 20425491]
- Shahian DM & Grover FL, 2014 Biomarkers and risk models in cardiac surgery. *Circulation*, 130, 932–5. [PubMed: 25098241]
- Shimpo M, Morrow DA, Weinberg EO, Sabatine MS, Murphy SA, Antman EM & Lee RT, 2004 Serum levels of the interleukin-1 receptor family member ST2 predict mortality and clinical outcome in acute myocardial infarction. *Circulation*, 109, 2186–90. [PubMed: 15117853]
- Stundl A, Lunstedt NS, Courtz F, Freitag-Wolf S, Frey N, Holdenrieder S, Zur B, Grube E, Nickenig G, Werner N, Frank D & Sinning JM, 2017 Soluble ST2 for Risk Stratification and the Prediction

- of Mortality in Patients Undergoing Transcatheter Aortic Valve Implantation. *Am J Cardiol*, 120, 986–993. [PubMed: 28739033]
- Wang TJ, Wollert KC, Larson MG, Coglianese E, McCabe EL, Cheng S, Ho JE, Fradley MG, Ghorbani A, Xanthakis V, Kempf T, Benjamin EJ, Levy D, Vasan RS & Januzzi JL, 2012 Prognostic utility of novel biomarkers of cardiovascular stress: the Framingham Heart Study. *Circulation*, 126, 1596–604. [PubMed: 22907935]
- Wernly B, Lichtenauer M, Jirak P, Eder S, Reiter C, Kammler J, Kypta A, Jung C, Franz M, Hoppe UC, Landmesser U, Figulla HR & Lauten A, 2017 Soluble ST2 predicts 1-year outcome in patients undergoing transcatheter aortic valve implantation. *Eur J Clin Invest*, 47, 149–157. [PubMed: 28036122]
- Willems S, Sels JW, Flier S, Versteeg D, Buhre WF, De Kleijn DP, Hofer IE & Pasterkamp G, 2013 Temporal changes of soluble ST2 after cardiovascular interventions. *Eur J Clin Invest*, 43, 113–20. [PubMed: 23215810]

Clinical Significance:

Preoperative, postoperative, and pre-to-postoperative sST2 values can be used as a biomarker to identify adult patients at greatest risk of in-hospital mortality after CABG surgery.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Clinical Significance:

Preoperative, postoperative, and pre-to-postoperative soluble suppression of tumorigenicity 2 (sST2) values can be used as a biomarker to identify adults at greatest risk of in-hospital mortality after CABG surgery. Postoperative and pre-to-postoperative sST2 in combination with other established clinical risk factors for in-hospital mortality after CABG surgery can improve the ability of the surgical care team to more accurately identify the risks of CABG surgery. This improvement in prediction of early mortality can assist surgical care teams to determine, with the patient and their families, the most appropriate timing of surgery, surgical alternatives, and surgical and operative care approach.

Figure 1- Patient flow diagram.

NNE= Northern New England Cardiovascular Disease Study Group Biomarker Study,
sST2=Soluble suppression of tumorigenicity 2

Figure 2- ROC curves for clinical risk model with and without preoperative sST2 biomarker.

*Receiver operating characteristic (ROC) curve for the EuroSCORE II model without preoperative sST2 biomarker (dashed line) and the EuroSCORE II model with preoperative sST2 biomarker (solid line). The c-statistics for each model with 95% confidence intervals are listed in the figure (p-value= 0.9652).

Figure 3- ROC curves for clinical risk model with and without postoperative sST2 biomarker.

*Receiver operating characteristic (ROC) curve for the EuroSCORE II model without postoperative sST2 biomarker (dashed line) and the EuroSCORE II model with postoperative sST2 biomarker (solid line). The c-statistics for each model with 95% confidence intervals are listed in the figure (p-value= 0.0213).

Figure 4- ROC curves for clinical risk model with and without pre-to-postoperative sST2 biomarker.

*Receiver operating characteristic (ROC) curve for the EuroSCORE II model without pre-to-postoperative sST2 biomarker (dashed line) and the EuroSCORE II model with pre-to-postoperative sST2 biomarker (solid line). The c-statistics for each model with 95% confidence intervals are listed in the figure (p-value= 0.0215).

Figure 5- Association of sST2 and In-Hospital Mortality after Coronary Artery Bypass Grafting Surgery

* Patients in the third tercile of pre-, post-, and pre-to-postoperative sST2 values had significantly higher odds ($P < 0.05$) of in-hospital death compared to patients in the first tercile.† Adjustment was carried out using the EuroSCORE II mortality risk model, which includes age, sex, COPD, poor mobility secondary to musculoskeletal or neurological dysfunction, previous cardiac surgery, serum creatinine $>200 \mu\text{mol/L}$, critical preoperative state, unstable angina, LV dysfunction moderate or LVEF 30–50%, LV dysfunction poor or LVEF <30 , recent myocardial infarction, pulmonary hypertension, emergent priority, and other isolated CABG surgery.

Table 1.

Preoperative and postoperative sST2 (ng/mL) cut-off values

		Preoperative sST2 (n=1,560)	Postoperative sST2 (n=1,173)	Pre-to-postoperative sST2 (n=1,173)
Overall	Median (IQR)	3.8 (2.9, 5.3)	45.2 (25.2, 76.4)	40.9 (20.7, 71.1)
	Second tercile cut-off	3.2	31.3	26.8
	Third tercile cut-off	4.7	63.5	58.6
Alive at discharge	Median (IQR)	3.8 (2.9, 5.2)	44.6 (24.9, 75.0)	40.2 (20.3, 69.8)
	Second tercile cut-off	3.2	31.3	29.4
	Third tercile cut-off	4.7	63.5	66.1
Deceased at discharge	Median (IQR)	5.0 (4.1, 7.0)	149.1 (73.7, 310.8)	144.6 (66.0, 259.0)
	Second tercile cut-off	3.5	45.3	51.9
	Third tercile cut-off	4.8	67.2	67.4

sST2= Soluble suppression of tumorigenicity 2; ng/mL= nanogram/milliliter; IQR= Interquartile range

Table 2.

Patient characteristics and preoperative sST2 tercile distribution (n=1,560)

	Overall (%)	Alive at Discharge (%)	Deceased at Discharge (%)	P-value
AKIN stage				<0.001
No AKI	64.9%	65.8%	12.0%	
1	29.8%	29.9%	24.0%	
2	2.9%	2.6%	20.0%	
3	2.4%	1.7%	44.0%	
Age (years) *	65.3±10.1	64.0±10.1	65.7±9.6	<0.001
Female	23.7%	23.2%	46.9%	0.002
BMI *	29.7±5.6	29.7±5.5	29.0±6.1	0.4804
BSA *	2.0±0.2	2.0±0.2	1.9±0.3	0.0116
Smoker	22.7%	22.7%	21.9%	0.915
CHF	10.6%	10.5%	18.8%	0.163
Last preoperative creatinine *	1.2±1.0	1.1±1.0	1.5±1.1	0.0647
Diabetes	37.2%	37.3%	34.4%	0.734
EF < 40	11.0%	11.0%	11.1%	0.983
Hypertension	80.7%	80.0%	75.0%	0.411
Preoperative IABP	4.0%	3.8%	15.6%	<0.001
MI in last 7 days	20.5%	20.4%	25.0%	0.525
Any vascular disease	27.1%	26.8%	41.9%	0.061
Unstable angina	54.9%	54.4%	78.1%	0.008
COPD	13.0%	12.6%	28.1%	0.010
LM stenosis	29.8%	29.7%	34.4%	0.568
Prior CABG	2.3%	2.1%	13.3%	<0.001
Priority				0.082
Emergent	1.9%	1.9%	3.1%	
Urgent	67.8%	67.4%	84.4%	
Non-urgent	30.3%	30.7%	12.5%	
Received transfused blood	38.2%	37.2%	84.4%	<0.001
pRBCs transfused preoperatively				0.002
0	98.0%	99.0%	99.2%	
1	0.6%	0.4%	0.2%	
2	1.0%	0.6%	0.4%	
3 or more	0.5%	0.0%	0.2%	

* Mean ± interquartile range reported. sST2=Soluble suppression of tumorigenicity 2, AKI=acute kidney injury, AKIN=Acute Kidney Injury Network, BMI=body mass index (kg/m²), BSA=body surface area (m²), CHF=congestive heart failure, IABP=intra-operative balloon pump, MI=myocardial infarction, COPD=chronic obstructive pulmonary disease, LM stenosis= left main (LM) coronary artery stenosis CABG=coronary artery bypass graft, PCI=percutaneous coronary intervention, pRBC=packed red blood cell

Table 3.

In-hospital outcomes by terciles of preoperative ST2 measurements (n=1,560)

	First tercile N (%)	Second tercile N (%)	Third tercile N (%)	p value
sST2 tercile range (ng/mL)	(0.9–3.1)	(3.2–4.6)	(4.7–109.7)	
In-hospital mortality	5 (1.0)	8 (1.5)	19 (3.6)	0.006
Atrial fibrillation	94 (18.2)	115 (22.2)	118 (22.5)	0.155
Renal failure	1 (0.2)	2 (0.4)	8 (1.5)	0.021
Mediastinitis	0 (0.0)	6 (1.2)	8 (1.5)	0.024
Transient ischemic attack	3 (0.6)	1 (0.2)	1 (0.2)	0.444
Stroke	2 (0.4)	13 (2.5)	15 (2.9)	0.007
Low cardiac output	21 (4.1)	34 (6.7)	43 (8.4)	0.021
Pneumonia	5 (1.0)	13 (2.5)	18 (3.4)	0.027
Return to OR for bleeding	9 (1.7)	4 (0.8)	10 (1.9)	0.261
Leg wound infection	1 (0.2)	6 (1.2)	7 (1.3)	0.110

sST2=Soluble suppression of tumorigenicity 2, OR=operating room

Table 4.

Unadjusted operative sST2 values and adjusted sST2 values with the EuroSCORE II mortality model.

	Unadjusted Biomarker		Adjusted Biomarker with EuroSCORE II *	
	Odds ratio	p value	Odds ratio	p value
Preoperative terciles				
1	1.00		1.00	
2	1.61 (0.52 – 4.95)	0.407	1.53 (0.49 – 4.75)	0.462
3	3.86 (1.43 – 10.42)	0.008	3.87 (1.43 – 10.46)	0.008
Postoperative terciles				
1	1.00		1.00	
2	0.48 (0.04 – 5.31)	0.549	0.44 (0.04 – 4.94)	0.507
3	8.57 (1.97 – 37.34)	0.004	7.87 (1.80 – 34.54)	0.006
Pre-to-postoperative difference terciles				
1	1.00		1.00	
2	0.50 (0.04 – 5.51)	0.569	0.46 (0.04 – 5.12)	0.526
3	8.79 (2.02 – 38.33)	0.004	8.10 (1.85 – 35.51)	0.006

* Adjusted for: age, sex, ejection fraction, number of diseased vessels, left main stenosis, left main stenosis, white blood cell count, myocardial infarction, urgent priority, emergent priority, prior coronary artery bypass graft, peripheral vascular disease, any diabetes, renal failure, renal failure or preoperative serum creatinine, and COPD. Analyses with a preoperative only endpoint include 1,560 patients. Analyses that include postoperative endpoints include 1,173 patients. sST2 tercile ranges (ng/mL) are preoperative: tercile 1=(.9–3.1), tercile 2=(3.2–4.7), tercile 3=(4.7–109.7), postoperative: tercile 1=(0.2–31.2), tercile 2=(31.3–63.4), tercile 3=(63.5–545.7), pre-to-postoperative: tercile 1=(–70.4–26.7), tercile 2=(26.8–58.5), tercile 3=(58.6–542.8). sST2=Soluble suppression of tumorigenicity 2.

Table 5.

In-hospital outcomes by terciles of postoperative ST2 (n=1,173)

	First tercile N (%)	Second tercile N (%)	Third tercile N (%)	p value
sST2 tercile range (ng/mL)	(0.2–31.2)	(31.3–63.4)	(63.5–545.7)	
In-hospital mortality	2 (0.5)	1 (0.3)	17 (4.3)	<0.001
Atrial fibrillation	68 (17.8)	101 (25.5)	89 (22.6)	0.034
Renal failure	1 (0.3)	0 (0.0)	9 (2.3)	0.001
Mediastinitis	1 (0.3)	4 (1.0)	4 (1.0)	0.387
Transient ischemic attack	0 (0.0)	2 (0.5)	2 (0.5)	0.379
Stroke	4 (1.0)	6 (1.5)	13 (3.3)	0.056
Low cardiac output	12 (3.2)	18 (4.7)	46 (11.9)	<0.001
Pneumonia	3 (0.8)	4 (1.0)	21 (5.3)	<0.001
Return to OR for bleeding	4 (1.0)	4 (1.0)	10 (2.5)	0.138
Leg wound infection	0 (0.0)	3 (0.8)	8 (2.0)	0.012

sST2=Soluble suppression of tumorigenicity 2, AKI=acute kidney injury, AKIN=Acute Kidney Injury Network, OR=operating room