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Association of plasma soluble ST2 and galectin-3 with cardiovascular events and mortality following cardiac surgery

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Abstract

Background: Cardiac surgery induces hemodynamic stress on the myocardium, and this process can be associated with significant post-operative morbidity and mortality. Soluble suppression of tumorigenicity 2 (sST2) and galectin-3 (gal-3) are biomarkers of myocardial remodeling and fibrosis; however, their potential association with post-operative changes is unknown.

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Declarations of interest: S.G.C. and C.R.P. are on the Advisory Board of RenalytixAI, and both own equity in the same. S.G.C. has served as a consultant for AKI therapeutics for Quark Biopharma and CHF Solutions. The remaining authors have no disclosures.

Methods: We measured peri-operative plasma sST2 and gal-3 levels in two prospective cohorts (TRIBE-AKI and NNE) of over 1800 patients who underwent cardiac surgery. sST2 and gal-3 levels were evaluated for association with a composite primary outcome of cardiovascular event or mortality over median follow-up periods of 3.4 and 6.0 years, respectively, for the two cohorts. Meta-analysis of hazard ratio estimates from the cohorts was performed using random effects models.

Results: Cohorts demonstrated event rates of 70.2 and 66.8 per 1000 person-years for the primary composite outcome. After adjustment for clinical covariates, higher post-operative sST2 and gal-3 levels were significantly associated with cardiovascular event or mortality [pooled estimate HRs: sST2 1.29 (95% CI 1.16, 1.44); gal-3 1.26 (95% CI 1.09, 1.46)]. These associations were not significantly modified by pre-operative congestive heart failure or AKI.

Conclusions: Higher post-operative sST2 and gal-3 values were associated with increased incidence of cardiovascular event or mortality. These two biomarkers should be further studied for potential clinical utility for patients undergoing cardiac surgery.

Keywords

sST2; gal-3; biomarker; cardiac surgery; peri-operative; post-operative mortality; post-operative cardiovascular event; Meso assay

Introduction

Over the past four decades, there has been a decline in death from cardiovascular disease in the United States[1-3]. From 1980-2000, it is estimated that 47% of this decline was attributable to evidence-based medical and surgical treatments[4]. However, despite advances in technology and pre-surgical optimization, cardiac surgery continues to be associated with significant post-operative morbidity and mortality[5]. Clinicians may benefit from additional tools to predict post-operative outcomes or to identify patients for whom the benefit of surgery outweighs associated risk.

Blood biomarkers are ideally easily measurable, inexpensive, accurate, and indicative of a specific pathophysiologic finding[6]. Cardiac troponins and natriuretic peptides (brain natriuretic peptide, or BNP, and its N-terminal fragment, NT-proBNP) are among the most well-known biomarkers used in diagnosis and assessment of patients presenting with acute coronary syndromes and heart failure[7-11]. They associate with mortality in acute coronary syndromes and after cardiac surgery[12, 13]. More recently, soluble ST2 (sST2) and galectin-3 (gal-3) have been described as novel cardiac biomarkers with FDA-approved assays for clinical use in patients with heart failure. sST2 is a member of the interleukin-1 (IL-1) receptor family that serves as a decoy for IL-33, interfering with IL-33's ability to protect against hypertrophy and fibrosis[14-16]. Gal-3 is released from activated macrophages and is a global marker of inflammation and fibrosis[17-19]. These biomarkers are included in the American College of Cardiology Foundation/American Heart Association guidelines (class IIb) to risk stratify patients with heart failure[6, 11, 20-22]. Since they are mechanistically involved in remodeling and fibrosis, we sought to explore the applicability of sST2 and gal-3 as biomarkers for patients undergoing cardiac surgery.

Cardiac surgery often entails clamping of major blood vessels and exposure of blood to the extracorporeal circuit, and is expected to initiate an inflammatory cascade. In some cases, there may be dysregulation or overactivation of the immune system, which could contribute to post-operative morbidity and mortality. We hypothesized that higher levels of sST2 and gal-3 following cardiac surgery would indicate fibrosis and/or maladaptive remodeling, and would be associated with post-operative cardiovascular event (CVD) or mortality. We conducted an ancillary study from a large adult population undergoing cardiac surgery across six academic medical centers in North America [the TRIBE-AKI cohort[23]] to study this hypothesis, and then performed a validation of the study results in a second cohort [the Northern New England Cardiovascular Disease Study Group, or NNE Biomarker Study[24]]. We performed meta-analysis of the results from the two cohorts to summarize the strengths of association of peri-operative biomarker levels with clinical outcomes.

Methods

Patient Cohorts

TRIBE-AKI: Detailed methods of the Translational Research Investigating Biomarker Endpoints in AKI (TRIBE-AKI) study have been previously described[23]. A total of 1601 patients undergoing cardiac surgery [coronary artery bypass grafting (CABG) or valve surgery] who were at high risk for developing AKI were prospectively enrolled at six academic medical centers in North America between July 2007 and December 2009. Ethylenediaminetetraacetic acid (EDTA) plasma specimens from these participants were collected pre-operatively (up to two months prior to surgery) and 0-6 hours post-operatively. Participants for whom long-term administrative data was not available (n=304) or for whom all biomarker measurements were not available (n=104) were excluded, leaving a total of 1193 participants in final analyses (Supplemental Figure 1a).

NNE: To evaluate the validity of our observed associations, we studied a second cardiac surgery cohort, the Northern New England Cardiovascular Disease Study Group (NNE Biomarker Study). Detailed information on this cohort has been described[24-27]. A total of 1690 patients undergoing cardiac surgery (primarily isolated CABG) across 8 hospitals in New Hampshire, Maine, and Vermont were included in the prospective observational cohort. Plasma specimens were collected pre-operatively (prior to incision) and approximately 24 hours after surgery. Patients for whom administrative data was not available (n=387), for whom other exclusion criteria were met (n=54), or for whom biomarker measurements were not available (n=589) were excluded, leaving 660 participants for the final analyses (Supplemental Figure 1b).

Outcome Definitions

TRIBE-AKI: The primary outcome for this study was a composite of cardiovascular event or all-cause mortality after discharge, with discharge being used as a follow-up time of zero. Mortality was assessed by calling participants' homes, reviewing hospital records, and utilizing the National Death Index for participants in the United States or the Institute for Clinical Evaluative Sciences (ICES) for participants in Canada. A cardiovascular event was defined as hospitalization for acute coronary syndrome, myocardial infarction, congestive

heart failure (CHF), coronary bypass, or percutaneous coronary intervention. Outcomes for American participants were obtained through linkages with the Center for Medicare and Medicaid Services databases, and for Canadian participants through data holdings at ICES. Cardiovascular events were identified using coding from the International Classification of Diseases (revisions 9 and 10) and the Canadian Classification of Health Interventions. Datasets were linked using unique, encoded identifiers, and analyzed at ICES. Accuracies of diagnostic codes have been previously published[28].

NNE: Cardiovascular events and all-cause mortality were obtained using Medicare in-patient claims, state all-payer in-patient claims using name, gender, social security number, date of birth, and zip-code of residence at the time of surgery, and the National Death Index. Maine and Vermont completed links internally. Probabilistic linking was used for New Hampshire all-payer in-patient claims. Complete ascertainment was achieved for Medicare, Vermont, and Maine. Five percent of New Hampshire patients were not matched in the New Hampshire in-patient claims[24, 25].

Biomarker Assays

A multiplex Meso Scale assay (Meso Scale Diagnostics, Rockville, MD) was used to measure sST2 and gal-3. Assay characteristics are provided in Supplemental Table 1. Meso Scale assays had excellent characteristics with linearity of dilution and spike and recovery experiments, though the gal-3 assay had lower correlation to its respective FDA-approved assay (sST2, r = 0.98; gal-3, r = 0.78).

Statistical Analyses

Descriptive statistics were reported as mean (95% confidence interval) or median (interquartile range) for continuous variables, and as frequency (percentage) for categorical variables. Biomarker concentrations were modeled continuously as log-transformed (base *e*) variables, and categorically as tertiles with the lowest tertile serving as the reference group. Cox proportional hazards regression models were used to estimate the associations between the studied biomarkers and time to the primary composite outcome. Kaplan Meier product limit curves were produced to graphically examine the association between biomarkers and the primary composite endpoint. The Kolmogorov-type supremum test was used to evaluate the proportional hazards assumption.

We adjusted models for the following covariates: Society of Thoracic Surgery (STS) score, sex, cardiopulmonary bypass time, non-elective surgery, hypertension, and CHF (any diagnostic coding for CHF). The STS score is a previously published score used to estimate the risk of post-operative morbidity and mortality in patients undergoing cardiac surgery, and is composed of pre-operative serum creatinine, age, surgery type, diabetes, chronic lung disease, recent myocardial infarction, race, reoperation, New York Heart Association class, and cardiogenic shock[29]. Chronic lung disease was not captured in the TRIBE-AKI study, and we therefore calculated the STS score with all participants coded as not having this condition. Where specified, data from the TRIBE-AKI cohort was also adjusted for NT-proBNP and cardiac troponin T (NT-proBNP and troponin T values were not available from the NNE cohort).

After exploring associations between biomarkers and outcomes in each cohort, we combined results of the two cohorts. We used Cochran's Q test statistic to test for heterogeneity between studies, and the I-squared statistic to quantify the magnitude of heterogeneity. A pooled estimate was not presented in cases where the Q test was statistically significant. Pooled hazard ratio estimates were calculated using the random effects meta-analysis method.

To determine if the associations between biomarkers and the primary outcome were modified by pre-operative CHF, interaction terms between each biomarker and CHF were included in the model. This modeling approach was also used to examine if AKI was an effect modifier.

Analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC) and R version 3.1.2 (R foundation for Statistical Computing, Vienna, Austria). Tests of significance were two-sided, with $p < 0.05$ considered significant.

Study Approval

Institutional review boards from each participating site approved this study and its protocols, and all participants or their surrogates provided written informed consent.

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The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Results

Baseline characteristics

The TRIBE-AKI and NNE cohorts respectively included 1193 and 660 patients, with median follow-up periods of 3.4 (2.4, 4.2) and 6.0 (3.9, 6.0) years. Table 1 a-b lists patient characteristics by tertile of post-operative sST2 and gal-3. Compared to the TRIBE-AKI cohort, patients of the NNE cohort had fewer pre-operative comorbidities (diabetes, hypertension, and CHF) but higher prevalence of prior myocardial infarction, and were less likely to have an elective surgery (28% in NNE versus 86% in TRIBE-AKI). The majority of NNE patients underwent isolated CABG, with only 5% receiving CABG with valve repair compared to 24% of TRIBE-AKI patients. Post-operative gal-3 levels were lower in men, and sST2 and gal-3 levels were higher in patients with pre-existing CHF. Post-operative sST2 and gal-3 levels were higher in patients who underwent CABG with valve repair, and in those with longer perfusion times or hospitalizations. Biomarkers were lower in patients who had been scheduled for elective surgery. Baseline and clinical characteristics by pre-operative biomarker levels were similar to post-operative findings and are presented in Supplemental Table 2 a-b.

Association of biomarkers with the primary composite outcome

Event rates for the primary composite outcome were 70.2 and 66.8 per 1000 person-years for the TRIBE-AKI and NNE cohorts, respectively, with approximately half of the events coming from cardiovascular events and half from deaths (Supplemental Table 3a). Biomarker values were approximately 1.5-fold higher following surgery (Supplemental Figure 2a-b). Event curves of the primary outcome for TRIBE-AKI participants per year are shown in Figure 1 a-d, demonstrating increased probability of CVD or death for participants with higher values of sST2 pre- and post-operatively, and for higher values of gal-3 post-operatively.

Hazard ratios for the primary outcome using log-transformed sST2 and gal-3 values and tertiles are shown in Table 2. After adjustment for clinical covariates, there was a 69% higher risk of the primary outcome for each log-unit increase of pre-operative sST2 in the TRIBE-AKI cohort, and the highest tertile of pre-operative sST2 had a HR of 1.91 (95% CI 1.40, 2.60) for the primary outcome compared with the lowest tertile. However, the significance of this association was not confirmed by NNE cohort data. Post-operatively, TRIBE-AKI patients with the highest tertile of sST2 values had a two-fold risk (HR 2.0; 95% CI 1.44, 2.78) for the primary outcome compared to patients with the lowest tertile of sST2 values, with NNE patients demonstrating similar outcomes. Results for both biomarkers were comparable when looking at cardiovascular events alone, suggesting that cardiovascular events (largely driven by heart failure events) and death events likely contributed similarly to the reported association (Supplemental Table 3b). Post-operative associations remained unchanged after adjustment for pre-operative biomarker values (data not shown). In a subset analysis of the TRIBE-AKI cohort only, the highest tertile of sST2

remained significantly associated with the primary outcome even after added adjustments for NT-proBNP or troponin T (Supplemental Table 4). Combining data from both cohorts in a meta-analysis, pooled HR estimates demonstrated a 1.29-fold risk (95% CI 1.16, 1.44) for the primary outcome for each log-unit increase in post-operative sST2 (Figure 2 a-b). Spearman correlations between sST2 and gal-3 were 0.056 for pre-op values and 0.251 for post-op values, supporting the idea that these biomarkers do not always correlate in expression and may not be able to be used interchangeably.

In the TRIBE-AKI cohort, each log higher value of pre- or post-operative gal-3 was respectively associated with 14% or 22% higher risk of incidence CV event or mortality (Table 2). While the significance of this association was not maintained after adjustment for clinical covariates in the TRIBE-AKI cohort, the NNE cohort supported higher incidence of the primary outcome for the highest tertiles of pre- and post-operative gal-3 compared to the lowest tertiles [pre-op HR 1.50 (95% CI 1.05, 2.13), post-op HR 1.45 (95% CI 1.03, 2.06)]. Meta-analyses demonstrated a pooled 1.26-fold risk (95% CI 1.09, 1.46) for the primary outcome for each log-unit increase in post-operative gal-3 (Figure 2 c-d).

To evaluate the prognostic utility of pre-operative sST2 or gal-3 compared to STS scores, we then quantified c-indices (represented as areas under the curve or AUC), integrated discrimination index (IDI) scores, net reclassification index (NRI) scores, and reclassification proportions (Table 3). Use of pre-operative sST2, gal3, or both did not improve the prognostic utility of the STS score for 1-year or 3-year CVD or death, as demonstrated by similar AUC numbers and low IDI and NRI scores. However, use of biomarker values did capture some events that would not have been noted by STS score alone (events correctly reclassified), and did correctly reclassify non-events that would have otherwise been noted by a high STS score.

Association of biomarkers stratified by clinically important subgroups

We evaluated if our observed associations of sST2 and gal-3 with the primary outcome were modified by the prevalence of pre-operative CHF. There was no significant interaction between prevalence of CHF and the primary outcome for sST2 in either cohort (Supplemental Table 5). However, there was a significant interaction between pre-operative gal-3 and CHF status for the primary outcome, with a trend towards incidence of the primary outcome for patients with pre-operative CHF.

We also evaluated potential effect modification of AKI on the association of sST2 and gal-3 with the primary outcome. In the TRIBE-AKI cohort, there was an interaction between pre-operative gal-3 and AKI status for the primary outcome, as gal-3 appeared to associate with the primary outcome in patients without pre-operative AKI. However, this observation was not confirmed in the NNE cohort (Supplemental Table 6). There was no significant interaction between prevalence of AKI and the primary outcome for post-operative sST2 or gal-3 for the primary outcome in either cohort.

Discussion

In this study of adults undergoing cardiac surgery, we evaluated association of two cardiac biomarkers, plasma sST2 and gal-3, with a primary composite outcome of long-term cardiovascular event or all-cause mortality. We conclude that post-operative sST2 and gal-3 associate with the primary composite outcome, even after adjustment for clinical covariates, NT-proBNP, or troponin T. These findings were independent of pre-existing CHF or AKI.

Interestingly, higher pre-operative sST2 and gal-3 levels also demonstrated association with the primary outcome, though results had high heterogeneity. This finding raises questions regarding mechanisms and timing of biomarker expression and activity in cardiac tissue. Both sST2 and gal-3 have been studied in a variety of cardiac diseases including heart failure, atrial fibrillation, myocardial infarction, hypertrophy, and hypertension[30-35], and higher baseline levels could indicate more severe underlying cardiac dysfunction, which could contribute to future morbidity and mortality.

Though we studied associations between biomarker levels and clinical outcomes, our study did not address mechanisms by which these biomarkers influence the myocardium. Both biomarkers were first discovered to play a role in cardiac remodeling through large microarray analyses, with sST2 linked to myocardial injury in response to myocardial infarction[36], and gal-3 to cardiac dysfunction in hypertrophied rat hearts[19]. The specifics of their cellular actions, however, are yet to be fully understood and are complicated by multiple isoforms and protein structures, and by heterogeneous expression in tissues.

sST2, for instance, is one of three isoforms of the *ST2* gene (the other two being a membrane-bound ST2L receptor and a variant ST2)[16, 37, 38]. IL-33 is a functional ligand for ST2L and promotes release of inflammatory cytokines and chemokines. Abundance of sST2, which serves as a decoy for active IL-33 in the extracellular space, could aid in avoiding damage caused by excessive inflammation. In fact, sST2 reduces inflammation in models of AKI and renal ischemia reperfusion[39, 40]. However, in cardiac tissue, the IL-33/ST2L axis is cardioprotective in shielding against cardiomyocyte apoptosis and maladaptive hypertrophy, and sST2 is therefore considered to be harmful in blocking antihypertrophic effects of IL-33[14, 15]. Gal-3 has an even wider variety of expression patterns and functions[17, 18]. It is ubiquitously expressed in the digestive tract, kidneys, lungs, and heart, and has different effects in the cytoplasm, cell surfaces, and extracellular environment. Gal-3 levels are low in cardiac tissue but are upregulated during processes such as left ventricular hypertrophy and heart failure[19]. One proposed mechanism for gal-3 activity during cardiac hypertrophy is that macrophages release gal-3 to induce fibrosis via TGF-beta pathways[19, 35, 41-43].

The possibility of therapeutics targeting these biomarkers in the setting of cardiac surgery is also unclear. While blockade of IL-33 is studied in asthma[45, 46] and blockade of sST2 in graft-versus-host disease[47, 48], sST2 inhibition has not been studied in cardiac disease. Gal-3 inhibition is studied in cancer and nonalcoholic steatohepatitis[49-51], and the gal-3 inhibitor TD139 was FDA-approved for patients with idiopathic pulmonary fibrosis[50]. Gal-3 blockade mitigates cardiac remodeling in animal models[42, 43, 52], but there are not yet studies of gal-3

inhibition in patients with cardiac disease. The expression patterns and multifaceted roles of these biomarkers will make it challenging to ensure specificity of therapeutic targets, and studies of upstream and downstream modulators may help elucidate therapeutics targets to reduce the incidence of cardiovascular events and mortality.

Our study has several strengths, including that it is based on two multicenter, prospective studies, with broad participation of adults and high-quality data, sample collection, handling, and processing across study sites. It is the first study with a validation cohort to analyze the association of sST2 and gal-3 with future cardiac events and mortality in patients undergoing cardiac surgery. We demonstrated significant association of these biomarkers with the primary composite outcome even after adjustment for clinical covariates and NT-proBNP or troponin. Measurement of sST2 and gal-3 could provide additional prognostic value to these more traditional methods of assessment. Future studies could address the clinical applicability of sST2 and gal-3 measurement in patients undergoing cardiac surgery.

Our study does have several limitations. Most notably, while there are FDA-approved assays for sST2 and gal-3 for use in patients with heart failure, our study used Meso Scale assays and did not provide parameters for clinical use in patients undergoing cardiac surgery. Ultimately, clinical use would necessitate re-measurement of biomarker values using FDA approved assays. The studied biomarkers have been shown to vary by certain patient characteristics. Baseline sST2 levels are higher in men, elderly patients, and in patients with diabetes[53]. Gal-3 independently associates with age, gender (higher gal-3 values in women), eGFR, urinary albumin excretion, body mass index, NT-proBNP, serum cholesterol, and systolic blood pressure[54-58]. The majority of participants in the study cohorts were Caucasian males, and the original enrollment criteria for the TRIBE-AKI cohort were limited to patients at high risk for AKI[23]. A significant portion of the cohort populations was excluded from the final analyses (25% for TRIBE-AKI and 61% for NNE). Participants in the study cohorts had an average age over 70, and our data may not be applicable to younger patients undergoing surgery. Though withdrawal from Medicare or emigration from Canadian provinces is rare, it is possible that 100% administrative follow-up was not achieved.[59, 60] Noted differences in patient population and characteristics between TRIBE-AKI and NNE (including type of surgery) limit direct comparison of these cohorts, and differences in sampling times as detailed in the methods section may limit the precision of reported associations. Furthermore, troponin T and NT-proBNP values were not measured in patients from the NNE cohort, limiting our ability to conclude that sST2 and gal-3 definitively remain associated with the primary outcome after adjustment for these traditional markers of cardiac risk.

In summary, we provide the first evidence for association of post-operative sST2 and gal-3 measurement in patients undergoing cardiac surgery, demonstrating that expression of these biomarkers is linked to cardiovascular event or mortality. We suggest that the prognostic value of sST2 and gal-3 is additive to risk associated with traditional covariates, NT-proBNP, and cardiac troponin T. However, further data from a large clinical trial would be necessary to assess clinical utility of these biomarkers. We propose that post-operative sST2 and gal-3 levels be evaluated as a tool to guide risk assessment for patients undergoing cardiac surgery.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights:

- Higher sST2 and gal-3 values associate with post-op mortality
- Association was shown in two independent patient cohorts
- Association is independent of heart failure or acute kidney injury
- sST2 and gal-3 measurement may supplement traditional markers of injury such as troponin T and NT-proBNP

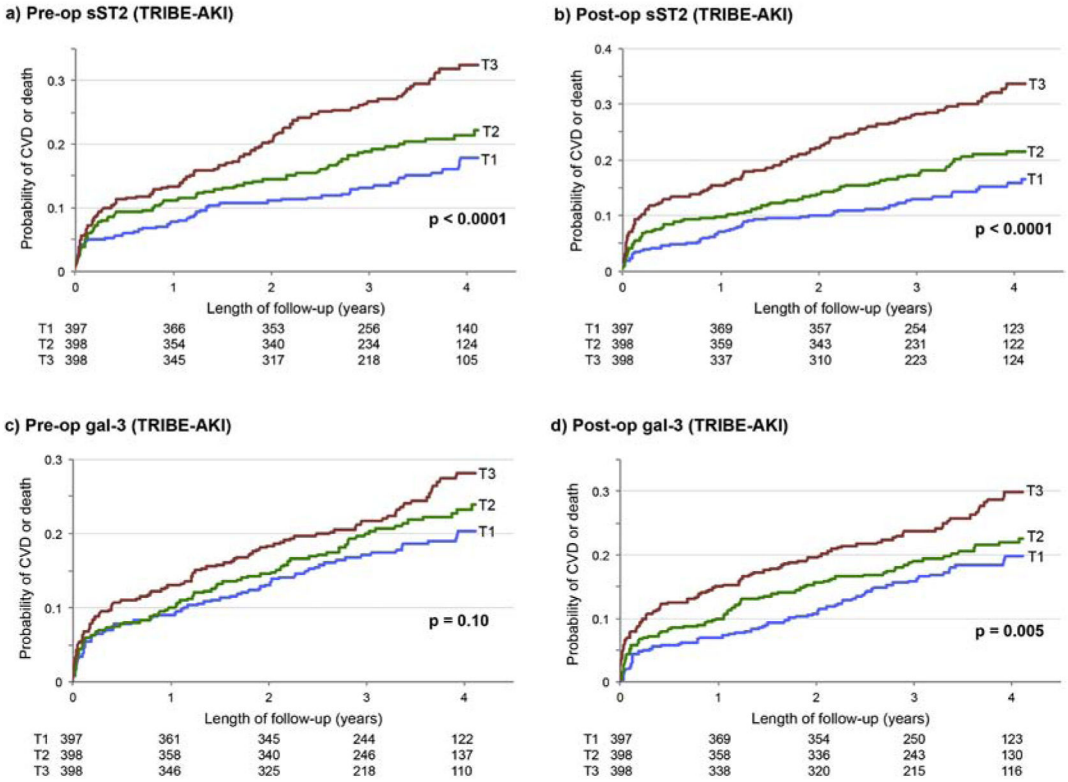

Figure 1.

a-d. Event curves by tertiles of pre- and post- operative sST2 and gal-3 for the TRIBE-AKI cohort. Higher tertiles of pre- and post- operative sST2 levels (a, b) and gal-3 levels (c, d) demonstrate association with higher event frequency, though this trend was not significant for pre-operative gal-3. Numbers of patients at risk per year for each tertile are listed below each graph.

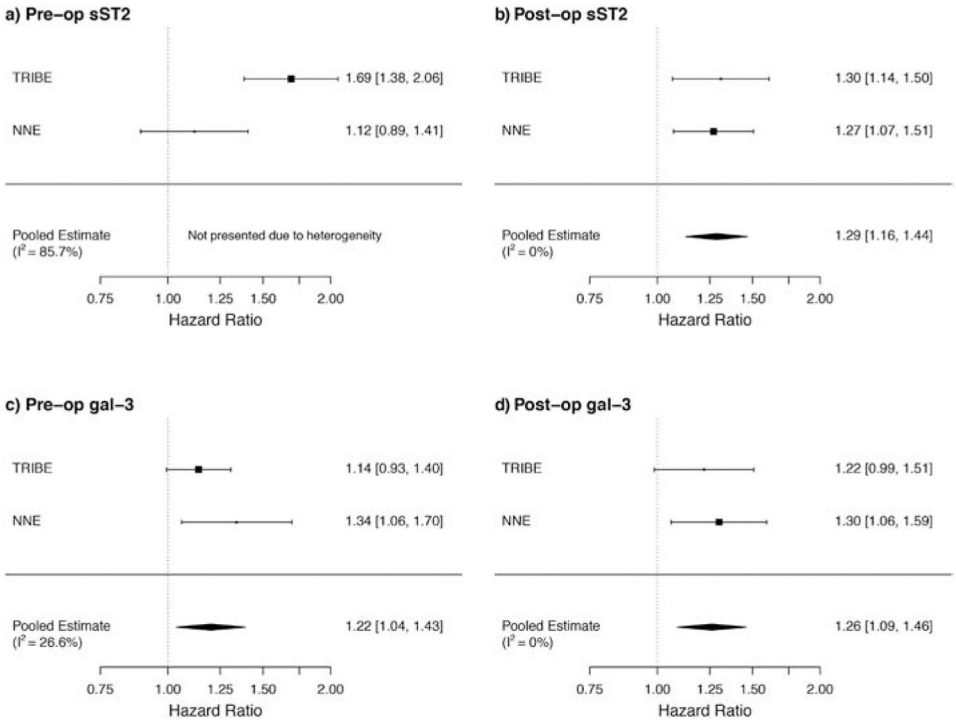

Figure 2.

a-d. Pooled hazard ratios for the primary composite outcome. HRs by pre- and post-operative (a, b) sST2 and (c, d) gal-3 values are shown, with pooled estimates and I^2 values. TRIBE-AKI: n=1193 with 70.2 events per 1000 person-years. NNE: n=660 with 66.8 events per 1000 person-years.

Table 1 a-b.

Characteristics of patient cohorts by post-operative sST2 and gal-3.

Numbers are provided as percentages or interquartile ranges. **a)** Tertiles are defined for sST2 as follows. For TRIBE-AKI: tertile 1 (T1) 0.6 – 4.2, tertile 2 (T2) 4.2 – 7.3, tertile 3 (T3) 7.3 – 357.3 in ng/ml. For NNE: tertile 1 (T1) 0.2 – 34.7, tertile 2 (T2) 34.8 – 67.1, tertile 3 (T3) 67.5 – 408.4 in ng/ml. **b)** Tertiles are defined for gal-3 as follows. For TRIBE-AKI: tertile 1 (T1) 0.4 – 9.7, tertile 2 (T2) 9.7 – 16.1, tertile 3 (T3) 16.1 – 81.5 in ng/ml. For NNE: tertile 1 (T1) 0.5 – 8.7, tertile 2 (T2) 8.7 – 14.4, tertile 3 (T3) 14.4 – 390.2 in ng/ml.

a: Characteristics of patient cohorts by post-operative sST2.

Patient characteristics	Post-operative sST2 (TRIBE-AKI)					Post-operative sST2 (NNE)				
	All (N=1193)	T1 (n=397)	T2 (n=398)	T3 (n=398)	p-value	All (N=660)	T1 (n=217)	T2 (n=221)	T3 (n=222)	p-value
Age at surgery (SD)	73 (8.4)	74 (8.2)	73 (8.2)	73 (8.8)	0.08	71 (7.9)	70 (8.4)	71 (7.2)	72 (8.0)	0.02
Male	837 (70%)	263 (66%)	288 (72%)	286 (72%)	0.1	501 (76%)	171 (79%)	164 (74%)	166 (75%)	0.5
Preoperative comorbidities										
Diabetes	444 (37%)	130 (33%)	171 (43%)	143 (36%)	0.01	273 (41%)	80 (37%)	93 (42%)	100 (45%)	0.2
Hypertension	955 (80%)	308 (78%)	321 (81%)	326 (82%)	0.3	555 (84%)	181 (83%)	188 (85%)	186 (84%)	0.9
Myocardial infarction	302 (26%)	112 (28%)	101 (26%)	90 (23%)	0.2	309 (47%)	87 (40%)	104 (47%)	118 (53%)	0.02
Congestive heart failure	244 (20%)	62 (16%)	62 (16%)	120 (30%)	<0.001	86 (13%)	22 (10%)	20 (9%)	44 (20%)	0.001
Preoperative renal function										
Serum creatinine	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)	1.1 (0.4)	0.2	1.2 (0.7)	1.2 (0.9)	1.1 (0.5)	1.3 (0.8)	0.1
≥ 90	129 (11%)	41 (10%)	42 (11%)	46 (12%)		95 (14%)	31 (14%)	38 (17%)	26 (12%)	
eGFR (ml/min per 1.73 m^2)	661 (55%)	224 (56%)	228 (57%)	209 (53%)	0.6	358 (54%)	123 (57%)	115 (52%)	120 (54%)	0.05
≤ 60	403 (34%)	132 (33%)	128 (32%)	143 (36%)		207 (31%)	63 (29%)	68 (31%)	76 (34%)	
Characteristics of surgery and hospitalization										
Elective surgery	1023 (86%)	350 (88%)	346 (87%)	326 (82%)	0.03	183 (28%)	72 (33%)	66 (30%)	45 (20%)	0.007
CABG with valve repair	285 (24%)	59 (15%)	100 (25%)	126 (32%)	<0.001	34 (5%)	**	**	**	**
CABG	576 (48%)	234 (59%)	211 (53%)	131 (33%)		618 (94%)	209 (96%)	203 (92%)	206 (93%)	
Valve	331 (28%)	105 (26%)	87 (22%)	139 (35%)		8 (1%)	**	**	**	**
On-Pump	1074 (90%)	342 (86%)	359 (90%)	373 (94%)	0.001	630 (95%)	204 (94%)	208 (94%)	218 (98%)	0.9
Perfusion time (min)	104 (80, 140)*	88 (70, 108)	100 (79, 129)	134 (104, 175)	<0.001	104 (87, 122)	96 (78, 113)	103 (89, 122)	111 (96, 130)	<0.001
Days hospitalized	6 (5, 9)	6 (5, 8)	6 (5, 8)	7 (6, 10)	<0.001	8 (6, 12)	7 (6, 10)	8 (7, 12)	10 (7, 15)	<0.001
Acute Kidney Injury	419 (35%)	96 (24%)	140 (35%)	183 (46%)	<0.001	273 (41%)	60 (27%)	87 (39.3%)	126 (56%)	<0.001
Post-operative complications										

a: Characteristics of patient cohorts by post-operative sST2.

Patient characteristics	Post-operative sST2 (TRIBE-AKI)					Post-operative sST2 (NNE)				
	All (N=1193)	T1 (n=397)	T2 (n=398)	T3 (n=398)	p-value	All (N=660)	T1 (n=217)	T2 (n=221)	T3 (n=222)	p-value
Stroke	7 (1%)	2 (1%)	2 (1%)	3 (1%)	0.87	**	**	**	**	**
Re-operation	57 (5%)	9 (2%)	10 (3%)	38 (10%)	<.001	26 (4%)	**	**	15 (2%)	**
Prolonged Ventilation	39 (3%)	3 (1%)	6 (2%)	30 (8%)	<.001	38 (6%)	**	12 (1%)	16 (2%)	**
DSWI	9 (1%)	3 (1%)	0	6 (2%)	0.05	4 (<%1)	**	**	**	**

b: Characteristics of patient cohorts by post-operative gal-3.

Patient characteristics		Post-operative gal-3 (TRIBE-AKI)					Post-operative gal-3 (NNE)				
		All (N=1193)	T1 (n=397)	T2 (n=398)	T3 (n=398)	p-value	All (N=660)	T1 (n=215)	T2 (n=222)	T3 (n=223)	p-value
Age at surgery (SD)		73 (8.4)	73 (8.3)	74 (8.6)	73 (8.3)	0.8	71 (7.9)	70 (7.2)	72 (7.2)	71 (9.0)	<0.001
Male		837 (70%)	296 (75%)	289 (73%)	252 (63%)	0.001	501 (76%)	185 (86%)	164 (74%)	152 (68%)	<0.001
Preoperative comorbidities											
Diabetes		444 (37%)	139 (35%)	153 (38%)	152 (38%)	0.5	273 (41%)	78 (36%)	91 (41%)	104 (47%)	0.09
Hypertension		955 (80%)	314 (79%)	313 (79%)	328 (82%)	0.3	555 (84%)	174 (81%)	190 (86%)	191 (86%)	0.3
Myocardial infarction		302 (26%)	103 (26%)	108 (27%)	92 (23%)	0.5	309 (47%)	103 (48%)	98 (44%)	108 (48%)	0.6
Congestive heart failure		244 (20%)	64 (16%)	73 (18%)	107 (27%)	<0.001	86 (13%)	18 (8%)	27 (12%)	41 (18%)	0.007
Preoperative renal function											
Serum creatinine		1.1 (0.3)	1.0 (0.3)	1.1 (0.3)	1.1 (0.4)	0.3	1.2 (0.7)	1.1 (0.5)	1.1 (0.4)	1.4 (1.1)	<0.001
eGFR (ml/min per 1.73 m^2)	≥90	129 (11%)	46 (12%)	43 (11%)	40 (10%)		95 (14%)	39 (18%)	29 (13%)	27 (12%)	
	60-90	661 (55%)	225 (57%)	226 (57%)	210 (53%)	0.5	358 (54%)	139 (65%)	118 (53%)	101 (45%)	<0.001
	≤60	403 (34%)	126 (32%)	129 (32%)	148 (37%)		207 (31%)	37 (17%)	75 (34%)	95 (43%)	
Characteristics of surgery and hospitalization											
Elective surgery		1023 (86%)	345 (87%)	351 (88%)	326 (82%)	0.03	183 (28%)	68 (32%)	61 (27%)	54 (24%)	0.2
CABG with valve repair		285 (24%)	78 (20%)	85 (21%)	122 (31%)	<0.001	34 (5%)	**	**	**	**
CABG		576 (48%)	226 (57%)	209 (53%)	141 (36%)		618 (94%)	198 (92%)	221 (>99%)	199 (84%)	
Valve		331 (28%)	93 (23%)	104 (26%)	134 (34%)		**	**	**	**	**
On-Pump		1074 (90%)	342 (86%)	351 (88%)	381 (96%)		630 (95%)	206 (96%)	212 (95%)	212 (95%)	
Perfusion time (min)		104 (80, 140)*	93 (71, 119)	99 (74, 130)	123 (98, 158)	<0.001	104 (87, 122)	98 (81, 117)	105 (88, 124)	108 (93, 123)	0.01
Days hospitalized		6 (5, 9)	6 (5, 8)	6 (5, 8)	7 (6, 10)	<0.001	8 (6, 12)	8 (6, 10)	8 (6, 11)	10 (7, 14)	0.01
Acute Kidney Injury		419 (35%)	106 (27%)	131 (33%)	182 (46%)		273 (41%)	70 (33%)	83 (37%)	120 (53%)	<0.001

b: Characteristics of patient cohorts by post-operative gal-3.

Patient characteristics	Post-operative gal-3 (TRIBE-AKI)					Post-operative gal-3 (NNE)				
	All (N=1193)	T1 (n=397)	T2 (n=398)	T3 (n=398)	p-value	All (N=660)	T1 (n=215)	T2 (n=222)	T3 (n=223)	p-value
Post-operative complication										
Stroke	7 (1%)	2 (1%)		5 (1%)	0.07	**	**	**	**	**
Re-operation	57 (5%)	17 (4%)	13 (3%)	27 (7%)	0.06	26 (4%)	**	14 (2%)	**	**
Prolonged Ventilation	39 (3%)	8 (2%)	8 (2%)	23 (6%)	0.003	38 (6%)	**	17 (2%)	14 (2%)	**
DSWI	9 (1%)	4 (1%)	2 (1%)	3 (1%)	0.70	**	**	**	**	**

[a] Information was not available for a small number of patients (less than 50).

** n < 11 with inability to pull data from the Medicare data server. SD = standard deviation; eGFR = estimated glomerular filtration rate; ICU = intensive care unit; DSWI = deep sternal wound infection.

Table 2.
Hazard ratios for the primary outcome by biomarker value.

Definitions of tertiles with n for each tertile are as listed in Table 1 and Supplemental Table 2.

Biomarker			Hazard Ratio (95% CI) of cardiovascular event or mortality					
			TRIBE-AKI			NNE		
			Event rate per 1000py	Unadjusted	Adjusted[a]	Event rate per 1000py	Unadjusted	Adjusted[a]
sST2	Pre-op	Log		1.85 (1.52, 2.25)	1.69 (1.38, 2.06)		1.33 (1.07, 1.66)	1.12 (0.89, 1.41)
		T1	48.5	1.0 *(referent)*	1.0 *(referent)*	52.11	1.0 *(referent)*	1.0 *(referent)*
		T2	64.8	1.31 (0.95, 1.82)	1.38 (0.99, 1.91)	70.22	1.34 (0.95, 1.89)	1.28 (0.91, 1.81)
		T3	100.2	2.00 (1.48, 2.70)	1.91 (1.40, 2.60)	78.51	1.49 (1.06, 2.10)	1.16 (0.82, 1.65)
	Post-op	Log		1.39 (1.23, 1.56)	1.31 (1.14, 1.50)		1.49 (1.24, 1.78)	1.27 (1.07, 1.51)
		T1	47.0	1.0 *(referent)*	1.0 *(referent)*	53.93	1.0 *(referent)*	1.0 *(referent)*
		T2	62.0	1.31 (0.94, 1.83)	1.32 (0.94, 1.85)	54.24	1.01 (0.70, 1.45)	0.98 (0.68, 1.40)
		T3	104.2	2.18 (1.61, 2.95)	2.00 (1.44, 2.78)	95.65	1.74 (1.26, 2.41)	1.43 (1.03, 1.99)
Gal-3	Pre-op	Log		1.24 (1.01, 1.53)	1.14 (0.93, 1.40)		1.52 (1.20, 1.91)	1.34 (1.06, 1.69)
		T1	59.4	1.0 *(referent)*	1.0 *(referent)*	45.41	1.0 *(referent)*	1.0 *(referent)*
		T2	69.1	1.17 (0.87, 1.59)	1.10 (0.81, 1.49)	74.87	1.62 (1.14, 2.30)	1.55 (1.09, 2.20)
		T3	82.7	1.39 (1.03, 1.87)	1.20 (0.89, 1.63)	83.44	1.79 (1.26, 2.54)	1.50 (1.05, 2.13)
	Post-op	Log		1.37 (1.11, 1.68)	1.22 (0.99, 1.51)		1.53 (1.26, 1.87)	1.30 (1.06, 1.58)
		T1	55.7	1.0 *(referent)*	1.0 *(referent)*	49.10	1.0 *(referent)*	1.0 *(referent)*
		T2	66.2	1.19 (0.87, 1.63)	1.15 (0.84, 1.57)	59.85	1.22 (0.85, 1.74)	1.03 (0.72, 1.49)
		T3	90.2	1.61 (1.20, 2.16)	1.35 (0.99, 1.85)	94.27	1.87 (1.34, 2.62)	1.45 (1.03, 2.06)

[a]Adjusted model included Society of Thoracic Surgery (STS) score, sex, cardiopulmonary bypass time, non-elective surgery, hypertension, and congestive heart failure.

Table 3.
Prognostic utility of sST2 and gal-3 compared to STS scores.

Due to the low event rate at 30 days, values were quantified for 1 and 3 years post-operatively. NRI calculations used thresholds to define low, medium and high risk. For 1-year outcomes the categories were defined as <7.5%, 7.5–15% and >15% and for 3-years <15%, 15–30% and >30%.

Outcome	Model	AUC	AUC difference	IDI (95% CI)	NRI (95% CI)	% Events correctly reclassified	% Non-events correctly reclassified
1-year CVD or death	STS score	0.60					
	STS + log pre-op sST2	0.63	0.03 (−0.003, 0.06)	0.0054 (0.001, 0.010)	0.086 (−0.003, 0.175)	7%	2%
	STS + log pre-op gal-3	0.61	0.002 (−0.01, 0.02)	0.0012 (−0.0005, 0.003)	0.008 (−0.045, 0.062)	2%	−2%
	STS + sST2 and gal-3	0.63	0.03 (−0.004, 0.06)	0.0064 (0.001, 0.012)	0.073 (−0.020, 0.167)	5%	3%
3-year CVD or death	STS score	0.61					
	STS + log pre-op sST2	0.66	0.05 (0.02, 0.08)	0.0222 (0.013, 0.033)	0.098 (0.015, 0.181)	1%	8%
	STS + log pre-op gal-3	0.61	−0.001 (−0.007, 0.006)	0.001 (−0.0005, 0.002)	−0.012 (−0.040, 0.015)	−2%	1%
	STS + sST2 and gal-3	0.66	0.05 (0.02, 0.08)	0.0226 (0.013, 0.032)	0.105 (0.023, 0.188)	1%	9%