Journal of the American Heart Association

ORIGINAL RESEARCH

Soluble Suppression of Tumorigenicity-2 Predicts Mortality and Right Heart Failure in Patients With a Left Ventricular Assist Device

Lieke Numan, MSc; Emmeke Aarts, PhD; Faiz Ramjankhan, MD; Marish I. F. Oerlemans, MD, PhD; Manon G. van der Meer, MD, PhD; Nicolaas de Jonge, MD, PhD; Anne-Marie Oppelaar, MSc; Hans Kemperman, PhD; Folkert W. Asselbergs, MD, PhD; Linda W. Van Laake, MD, PhD

BACKGROUND: Soluble suppression of tumorigenicity-2 (sST2) predicts mortality in patients with heart failure. The predictive value of sST2 in patients with a left ventricular assist device remains unknown. Therefore, we studied the relationship between sST2 and outcome after left ventricular assist device implantation.

METHODS AND RESULTS: sST2 levels of patients with a left ventricular assist device implanted between January 2015 and December 2022 were included in this observational study. The median follow-up was 25 months, during which 1573 postoperative sST2 levels were measured in 199 patients, with a median of 29 ng/mL. Survival of patients with normal and elevated preoperative levels was compared using Kaplan-Meier analysis, which did not differ significantly (P=0.22) between both groups. The relationship between postoperative sST2, survival, and right heart failure was evaluated using a joint model, which showed a significant relationship between the absolute sST2 level and mortality, with a hazard ratio (HR) of 1.20 (95% CI, 1.10–1.130; P<0.01) and an HR of 1.22 (95% CI, 1.07–1.39; P=0.01) for right heart failure, both per 10-unit sST2 increase. The sST2 instantaneous change was not predictive for survival or right heart failure (P=0.99 and P=0.94, respectively). Multivariate joint model analysis showed a significant relationship between sST2 with mortality adjusted for NT-proBNP (N-terminal pro-B-type natriuretic peptide), with an HR of 1.19 (95% CI, 1.00–1.42; P=0.05), whereas the HR of right heart failure was not significant (1.22 [95% CI, 0.94–1.59]; P=0.14), both per 10-unit sST2 increase.

CONCLUSIONS: Time-dependent postoperative sST2 predicts all-cause mortality after left ventricular assist device implantation after adjustment for NT-proBNP. Future research is warranted into possible target interventions and the optimal monitoring frequency.

Key Words: end-stage heart failure ■ left ventricular assist device ■ right heart failure ■ soluble suppression of tumorigenicity-2

Soluble suppression of tumorigenicity-2 (sST2) is a prognostic indicator for mortality in patients with heart failure and may help in risk stratification in patients with heart failure.[1] Although the mechanism has not been elucidated completely, it is known that sST2 is part of the suppression of tumorigenicity-2 (ST2)/interleukin 33 (IL-33) pathway, which is activated by increased cardiac wall stress.[2] Cardiac myocytes and lung epithelial cells are among the sources of sST2 production, enhanced by proinflammatory cytokines.[3,4]

Correspondence to: Lieke Numan, MSc, Department of Cardiology, University Medical Center Utrecht, Heidelberglan 100, 3584 CX Utrecht, the Netherlands. Email: l.numan-2@umcutrecht.nl

Preprint posted on MedRxiv, February 8, 2023. doi: https://doi.org/10.1101/2023.02.06.23285564.

This article was sent to Yen-Hung Lin, MD, PhD, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.123.029827

For Sources of Funding and Disclosures, see page 9.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Postoperative soluble suppression of tumorigenicity-2 is a predictor of all-cause mortality and right heart failure in patients with end-stage heart failure on left ventricular assist device support.
- Soluble suppression of tumorigenicity-2 predicts all-cause mortality after adjustment for N-terminal pro-B-type natriuretic peptide.

What Are the Clinical Implications?

- It is recommended to regularly measure soluble suppression of tumorigenicity-2 after left ventricular assist device implantation, and a closer follow-up in patients with elevated soluble suppression of tumorigenicity-2 levels may be warranted.

Nonstandard Abbreviations and Acronyms

HM3	HeartMate 3
HTx	heart transplantation
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
JM	joint model
LME	linear mixed effect
sST2	soluble suppression of tumorigenicity-2
ST2	suppression of tumorigenicity-2

Normally, IL-33 binds to the membrane-bound transmembrane isoform of ST2 and thereby prevents apoptosis and fibrosis. Soluble ST2 acts as a decoy receptor for IL-33, so the cardioprotective effect of IL-33 is lost when IL-33 binds to soluble ST2.[5]

In contrast to the general population with heart failure, only a few studies examined the role of sST2 in patients with end-stage heart failure. Left ventricular assist device (LVAD) implantation results in unloading of the left ventricle and promotes reverse modeling.[6] Despite improving survival and complication rates, patients on LVAD support have a relatively high mortality rate and frequently experience adverse events, such as right heart failure.[7,8] Hence, there is a continuous search for new biomarkers as a potential tool for early prediction and treatment. sST2 could contribute to stratification and early recognition of deterioration in patients on LVAD support. Tseng et al demonstrated high sST2 levels in patients with end-stage heart failure before LVAD implantation, especially in patients in cardiogenic shock at implantation. After LVAD implantation, sST2 levels decreased significantly, with normalized values after 3 months, suggesting that LVAD implantation leads to a reduction of fibrosis and inflammation.[9] Opfermann et al showed a significant increase in sST2 during the initial postoperative period after LVAD implantation and normalization to preoperative levels after 1 week and normal levels after 3 weeks.[10]

Although repeated sST2 measurements appeared to be a strong predictor of outcome in patients with acute heart failure,[11] the predictive value of serially measured sST2 levels in patients with an LVAD on long-term outcomes has not been elucidated yet. Therefore, we aimed to assess the relationship of serially measured sST2 and long-term outcome in patients on LVAD support in an observational and hypothesis-generating study. We hypothesized that elevated or increasing sST2 levels predict adverse outcome, such as right heart failure or death.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design

In this single-center retrospective cohort study, patients receiving a HeartWare or HeartMate 3 (HM3) between January 2015 and December 2021 in the University Medical Center Utrecht were included. The follow-up was until May 2022.

The study was approved by the local ethics committee of the University Medical Center Utrecht (No. 20-195) and was handled in accordance with the Declaration of Helsinki and Good Clinical Practice. We used the Strengthening the Reporting of Observational Studies in Epidemiology cohort checklist when writing our report.[12] The need for informed consent for the use of retrospective data was waived. Data were retrieved from the electronic health records.

End Points

The primary end points of the study were all-cause mortality and right heart failure. All-cause mortality was defined as follows: death or urgent heart transplantation (HTx) during follow-up. Transplantation was labeled as urgent HTx if a patient had received priority status on the waiting list (national 1A, national 1B, or international HU). Without the urgent HTx, the patient would probably not have survived, and we therefore considered this as an adverse outcome in addition to death. Patients were censored for ongoing support at the end

of follow-up, explantation, and nonurgent HTx. Right heart failure was defined using the definitions of the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) as follows: requiring right ventricular (RV) assist device support or NO inhalation or inotropic therapy for >1 week at any time after LVAD implantation. For the current study, we included the first right heart failure event >30 days postimplantation for analysis, because sST2 was mostly measured after the initial postoperative period.

sST2 Measurement

Both preoperative and postoperative sST2 levels were analyzed. sST2 was measured during regular outpatient visits (every 3–4 months) and from biobanked samples if available. Written informed consent was provided by patients who were included in the biobank. sST2 was measured in heparin plasma using the ASPECT-PLUS ST2 assay on an ASPECT Reader (Critical Diagnostics, San Diego, CA). Biobanked samples were centrifuged within 6 hours after withdrawal, and plasma was stored at −80 °C. Levels of sST2 using biobanked samples after a maximum of 1 freeze/thaw cycle were analyzed by using the Presage ST2 ELISA, according to manufacturer's instructions (Critical Diagnostics).[9] The ASPECT Reader and Presage ST2 ELISA techniques are comparable (R^2=0.92).[13]

Statistical Analysis

Preoperative sST2

We assessed survival (all-cause mortality) in patients with normal and elevated preoperative sST2 levels (cutoff, <35 ng/mL, which is used in patients with heart failure) using Kaplan-Meier analysis. As a sensitivity analysis, we used a cutoff of 27 ng/mL, which was demonstrated to be the best cutoff in patients with chronic heart failure for all-cause and cardiovascular death and heart failure hospitalization.[14] The last sST2 measurement within 30 days before the primary implantation was included.

Postoperative sST2

The intracluster correlation coefficient was calculated to express the variation of postoperative sST2 within patients and between patients. To visualize the trajectory of postoperative sST2, a heat map was created, which is a visualization technique (not for quantification) that shows the height of the average sST2 levels for all patients. Time bins of 90 days were used, and the heat map was sorted on patients with the highest sST2 measurement in the entire data set. Primary and secondary end points were indicated in the heat map.

In addition, we studied the association between longitudinal sST2 measurements and our primary and secondary end points using a joint model (JM) approach.[15] A JM approach was chosen because it deals with irregular measurement intervals and missing data and was used in comparable settings in previous studies.[16,17] Within this 2-step method, the trajectory of sST2 over time is combined with a time-to-event model. The longitudinal pattern of sST2 is estimated using linear mixed effect (LME) modeling. The LME model included a random effect for both the intercept and time, with patient identifier as the clustering level. A natural spline was used to allow for nonlinearity in the association between time and sST2, with a knot at 90 days. Four random cases were displayed, to visualize the estimated trajectory and the sST2 measurements. The accuracy of the predicted levels of sST2 was evaluated using the median square error of the LME model. Time-to-event analysis in the JM was done using 2 cause-specific multivariable Cox regression analyses for the primary and secondary outcome, stratified for device type (HeartWare or HM3), adjusting for clinically relevant variables: age at primary implantation, body mass index, sex, temporary mechanical support at primary implantation, INTERMACS score, ischemic cause, and RV function. RV function was classified as poor, moderate, or good by 2 independent cardiologists, who individually classified the RV based on echocardiography and right heart catheterization using earlier published methods.[18] Within the JM, both the effect of the predicted sST2 and the predicted change in sST2 at the time of the event (the instantaneous slope) on the primary and secondary outcome were assessed. As a sensitivity analysis, a multivariate JM analysis was performed, adjusted for serially measured NT-proBNP (N-terminal pro-B-type natriuretic peptide), with a $\log_{10}$ transformation of NT-proBNP and a natural spline with a knot at 90 days. In this multivariate JM, similar covariates as in the primary analysis were adjusted for.

In literature, patients who receive an HTx, including patients who were listed as high urgent, are usually censored. Hence, we performed a sensitivity analysis similar to the primary JM analysis, now also censoring for urgent HTx.

To assess whether postoperative sST2 trajectories vary in patients on different types of LVAD support (HeartWare or HM3), we fitted another separate LME model similarly to the LME model in the JM analysis and added device type as a fixed variable. Significance of the prediction of the sST2 trajectory by device type was assessed using a χ^2-log likelihood test comparing models with and without the predictor device type.

Preoperative and Postoperative sST2

To assess the correlation between preoperative sST2 and postoperative sST2, preoperative sST2 levels and predicted sST2 levels at the end of the follow-up were

visualized in a scatterplot. Moreover, to quantify this relationship, the Spearman correlation coefficient of the preoperative sST2 and predicted sST2 at the end of the follow-up or at the time of the event was calculated in all patients who were included in the primary JM analysis and in whom preoperative sST2 was available.

The flowchart of patients who were included for each of the analysis is displayed in the graphical abstract. Model assumptions of both linear mixed models and Cox regression were checked. $P<0.05$ was considered significant. Results are presented as median and interquartile range (IQR) for continuous variables and as number or percentage for categorical variables. All analyses were performed using R, version 3.6.3.

RESULTS

Between 2015 and January 2022, 237 patients received either HeartWare or HM3 as a primary LVAD implantation at the University Medical Center Utrecht. Baseline characteristics of all patients with and without postoperative sST2 measurement(s) are presented in Table 1, with complete covariates for all patients. The median age at implantation was 56 years (IQR, 16 years), and 65% of the patients were men. Most patients had nonischemic cardiomyopathy as an underlying disease (70%). The median follow-up time was 25 months (IQR, 33 months), during which 61 (26%) patients died after a median of 10 months (range, 0–69 months). Table 2 shows the causes of death. A total of 8 patients (3%) received urgent HTx after a median of 26 months (range, 1–66 months), 15 patients (6%) received normal HTx after a median of 36 months (range, 11–64 months), and no patients were weaned from LVAD support. Three patients received urgent HTx attributable to RV failure. Other reasons were as follows: obstructed outflow graft, recurrent driveline infection, recurrent pump thrombosis, or recurrent untreatable symptomatic ventricular tachycardia (leading to RV failure).

Right heart failure >30 days after surgery was diagnosed in 26 patients (11%). None of these patients were treated by a RV assist device implant.

Preoperative sST2

sST2 was measured preoperatively (<30 days before surgery) in 86 patients, with a median of 57 ng/mL (IQR, 57 ng/mL). Figure S1 depicts a box plot of the preoperative sST2 in patients who reached the primary end point and patients who did not. Table S1 shows the baseline characteristics of patients with and without preoperative sST2. Patients with preoperative sST2 level more often had a good RV function, more frequently received an implant with HM3, were less often on temporary mechanical support, and were more often classified as INTERMACS score 3 to 7. Figure 1 depicts the Kaplan-Meier survival of patients with high (>35 ng/mL in 64 patients) or normal (≤35 ng/mL in 21 patients) preoperative sST2 levels. Survival of patients with normal or elevated preoperative sST2 levels did not differ significantly ($P=0.22$). The sensitivity analysis with a cutoff of ≤27 ng/mL included 72 patients with elevated levels and 14 patients with normal sST2 levels (Figure S2). Similar to the primary Kaplan-Meier analysis, survival was not significantly different between the 2 groups ($P=0.14$).

Table 1. Baseline Characteristics of All Patients (n=237)

Characteristic	Value
Age, y	56 (46–62)
Male sex, n (%)	155 (65.4)
Ischemic cause, n (%)	72 (30.4)
Dilated cause, n (%)	149 (62.9)
BMI, kg/m^2	24.5 (21.8–27.5)
BSA, m^2	1.94 (1.80–2.09)
Right ventricular function, n (%)	
Poor	36 (15.2)
Moderate	126 (53.2)
Good	75 (31.6)
Device type, n (%)	
HeartWare	84 (35.4)
HeartMate 3	153 (64.6)
INTERMACS score, n (%)	
1	54 (22.8)
2	71 (30.0)
3–7	112 (47.3)
Preoperative temporary support, n (%)	42 (17.7)
Preoperative diabetes, n (%)	34 (14.3)
Preoperative eGFR, mL/min per 1.73 m^2	62 (46–87)
Preoperative bilirubin, μmol/L	19 (13–32)

Data are given as median (interquartile range) unless otherwise indicated. BMI indicates body mass index; BSA, body surface area; eGFR, estimated glomerular filtration rate; and INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support.

Postoperative sST2

In total, 1573 postoperative sST2 levels were measured in 199 patients, with a median of 29 ng/mL (IQR, 21 ng/mL). A total of 38 patients of 237 had no postoperative sST2 measurements, of which most died early. Postoperative sST2 measurements were displayed in a heat map (Figure S3), which suggests that most patients reaching the primary and secondary end points had a higher postoperative sST2 measurement. To test this finding, JM analysis was performed. Figure 2 depicts the postoperative sST2 measurement and its predicted trajectories by the LME model within the JM of 4 random cases. The median square error of the

Table 2. Causes of Death of All Patients (N=61)

Type of death	Patients, n (%)
Device malfunction	3 (4.9)
Infection	10 (16.4)
Multiorgan failure	12 (19.7)
Neurologic	13 (21.3)
Right heart failure	9 (14.8)
Other	14 (23.0)

predicted sST2 trajectories by the LME model was 4.5 ng/mL. The median square error of the predicted sST2 trajectories by the LME model was 4.5 ng/mL. All predicted sST2 trajectories are displayed in Figure 3, separated for patients with and without event (death, urgent HTx, right heart failure, or no event). The intracluster correlation coefficient of postoperative sST2 was 0.73, so 73% of the variation observed in postoperative sST2 is explained by differences between patients, and the remaining 27% is a result of variation within patients over time.

The JM confirmed the predictive value of time-dependent sST2 for survival with an HR of 1.20 (95% CI, 1.10–1.30; *P*<0.01) for a 10-unit increase in sST2 (Table 3). In addition, time-dependent sST2 was a predictor for right heart failure as well, with an HR of 1.22 (95% CI, 1.07–1.39; *P*=0.01) for a 10-unit increase. A sensitivity analysis where we censored for urgent transplantation, instead of considering it a proxy for mortality, confirmed the significant relation between time-dependent sST2 and survival, with an HR of 1.18 (95% CI, 1.08–1.30; *P*<0.01) for a 10-unit increase of sST2. Thus, higher expected levels of sST2 at a point in time are predictive for a worse survival. We also investigated whether the instantaneous dynamics of sST2 values at the time of the events would be more predictive than the time-dependent predicted values. However, the predicted instantaneous change in sST2 at the time of the event was not an independent predictor of survival (HR, 0.99 [95% CI, <0.01 to >10.0]; *P*=0.99) or of right heart failure (HR, 1.15 [95% CI, <0.01 to >10.0]; *P*=0.94).

In total, 1851 postoperative NT-proBNP levels were measured in 191 patients, with a median of 1457 ng/mL (IQR, 2095 ng/mL). Figure S4 depicts a histogram of all NT-proBNP values. In addition, the log10-transofmed NT-proBNP levels are displayed. Multivariate JM analysis, adjusted for serially measured NT-proBNP, showed

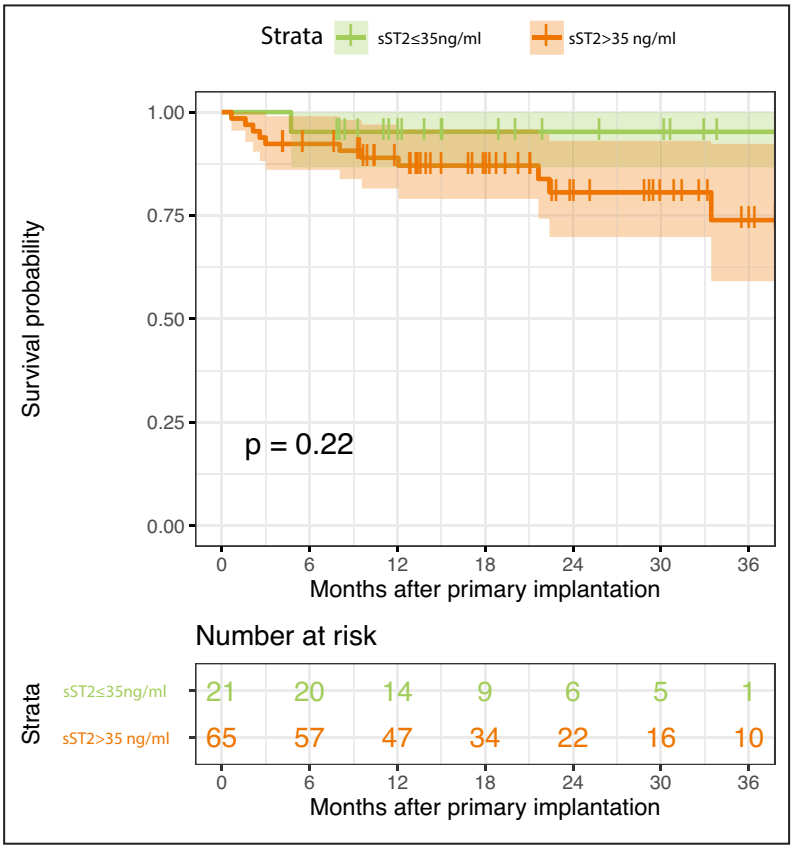

Figure 1. Kaplan-Meier survival.
Kaplan-Meier survival of patients with a normal (≤35 ng/mL) or elevated (>35 ng/mL) preoperative sST2 level (*P*=0.22). sST2 indicates soluble suppression of tumorigenicity-2.

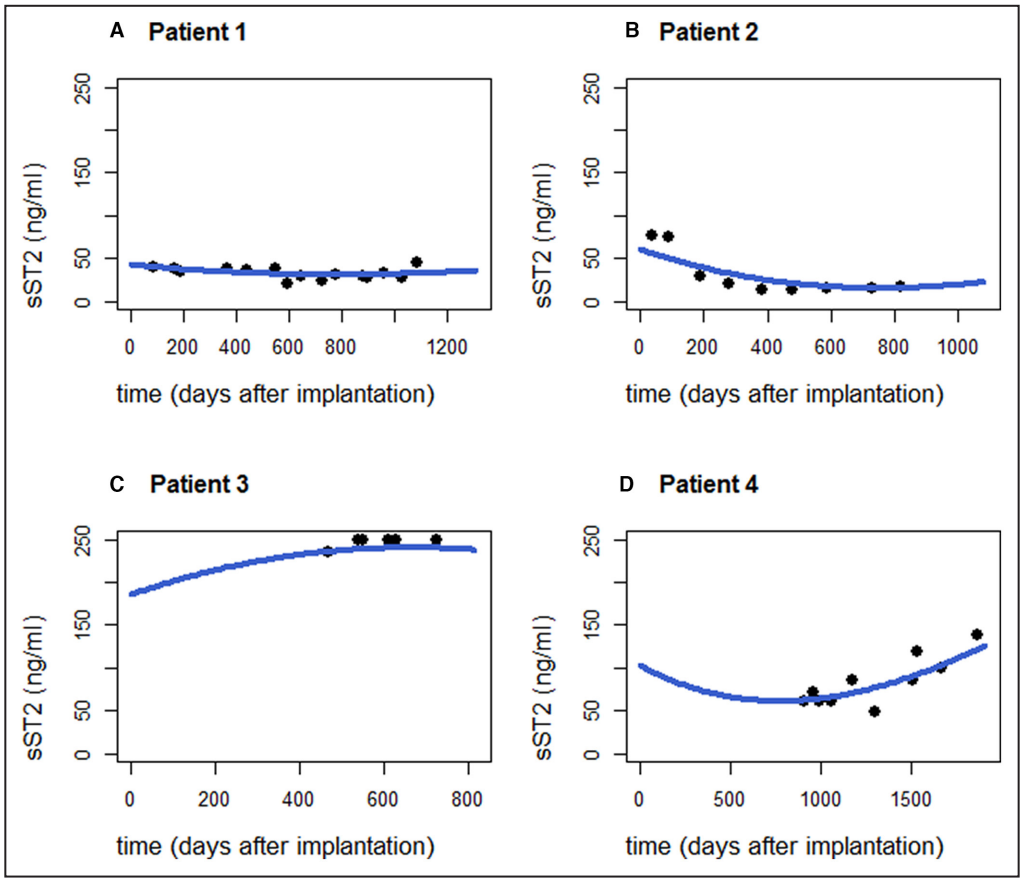

Figure 2. Postoperative sST2 levels.
A through **D**, Trajectory of postoperative sST2 levels (*y* axis) over time (*x* axis) in 4 randomly selected cases to show the results of the linear mixed model in individual patients. The black dots indicate the sST2 measurement, and the predicted sST2 trajectory by the linear mixed effects model is depicted by the blue line. Two patients who did not reach the primary end point (**A** and **B**) and 2 patients who reached the primary end point (**C** and **D**) were selected. sST2 indicates soluble suppression of tumorigenicity-2.

a significant relationship with mortality and urgent HTx with an HR of 1.19 (95% CI, 1.00–1.42; *P*=0.05) per 10-unit increase of time-dependent sST2. As an example, this means that the HR is 1.19 for an sST2 of 30 instead of 20 ng/mL. For right heart failure, the relationship was not significant after adjustment for NT-proBNP, with an HR of 1.22 (95% CI, 0.94–1.59; *P*=0.14) per 10-unit increase. In the multivariate JM, the HR of time-dependent NT-proBNP for mortality was 3.22 (95% CI, 0.62–16.5; *P*=0.14) for a NT-proBNP level that is 10 times higher. As an example, this implies an HR of 3.22 for an NT-proBNP of level of 2000 instead of 200 pg/mL. For right heart failure, the HR of time-dependent NT-proBNP was 2.18 (95% CI, 0.28–14.2; *P*=0.42) for an NT-proBNP level that is 10 times higher in the multivariate JM.

In addition, we explored the potential role of device type as a possible confounder for survival.[18,19] In a sensitivity analysis using the LME model with device type as additional fixed effect, device type was not a significant predictor of the trajectory of sST2 (*P*=0.26).

Finally, we studied the relation between preoperative sST2 and predicted postoperative sST2 at the event or end of the follow-up (Figure S5). The Spearman correlation coefficient of preoperative sST2 and predicted postoperative sST2 at the end of the follow-up was 0.05 (*P*=0.63).

DISCUSSION

In this study on long-term serial sST2 measurements in a large group of patients on LVAD support, we demonstrated that time-dependent sST2 levels after LVAD implantation are predictive for mortality and right heart failure. The time-dependent sST2 level was predictive for both right heart failure and mortality, whereas the instantaneous increase of sST2 at the event or end of the follow-up was not a significant predictor. In addition, time-dependent sST2 is a significant predictor for mortality adjusted for time-dependent NT-proBNP (graphical abstract). sST2 trajectories did not differ between patients on HM3 or HeartWare support. We

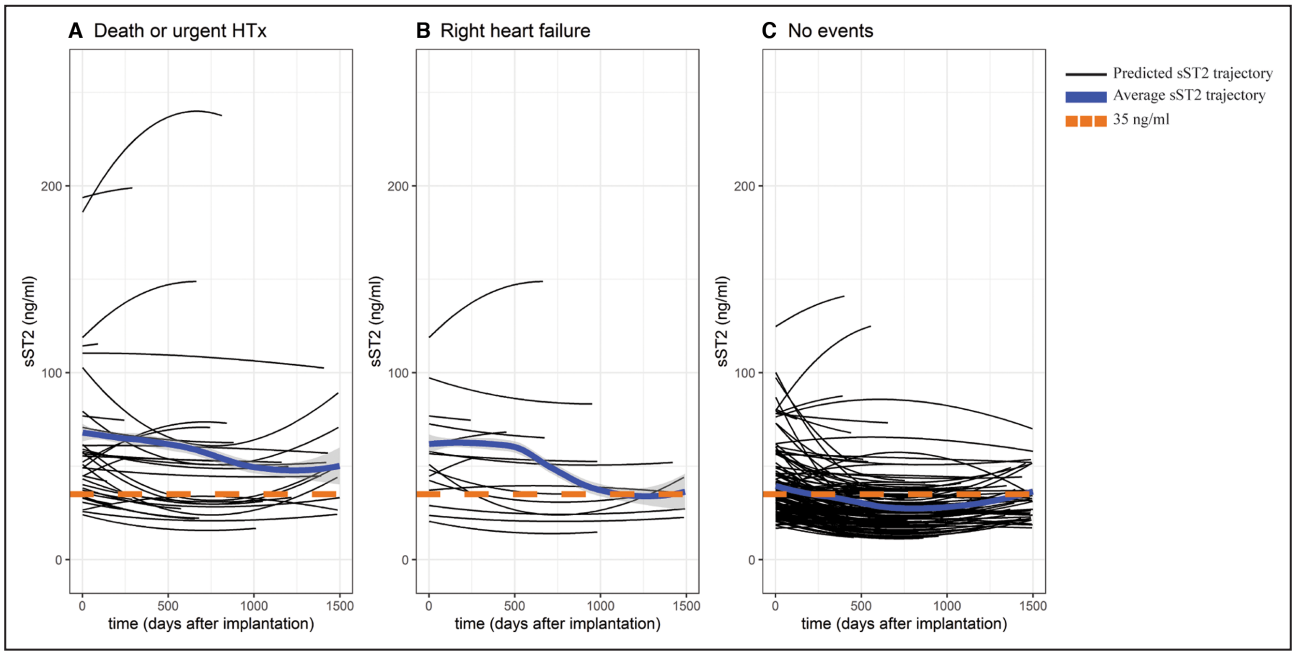

Figure 3. Predicted postoperative sST2.
Predicted postoperative sST2 trajectory of individual patients. The "normal" cutoff value (35 ng/mL) is indicated by the dashed orange line, and the blue line indicates the smoothened sST2 trajectory in each panel. Trajectories of patients who died or received urgent HTx (**A**), patients experiencing right heart failure (**B**), and patients without primary or secondary outcome (**C**). HTx indicates heart transplantation; and sST2, soluble suppression of tumorigenicity-2.

found no significant difference in survival on LVAD in patients with and without elevated preoperative sST2 levels.

sST2 has been studied extensively in patients with general heart failure for more than a decade.[5] Vark et al studied the prognostic value of serial sST2 measurements in patients with acute heart failure and suggested that an increase or stabilization of sST2 levels may be useful in daily practice for stratification or to monitor treatment.[11] Moreover, sST2 is an independent risk factor for hypertensive left ventricular hypertrophy.[20] Repeated sST2 measurements provide independent prognostic information in addition to NT-proBNP in patients with acute heart failure. As NT-proBNP is a biomarker indicating volume overload, whereas sST2 is a marker of remodeling, inflammation, and cardiac fibrosis, the 2 biomarkers are complementary.[11,21,22] sST2 levels may be increased in other, mostly inflammatory-associated diseases, such as chronic obstructive pulmonary disease, pneumonia, or sepsis.[23] However, in contrast to NT-proBNP, sST2 is independent of important prognostic factors, such as age, sex, body mass index, hypertension, smoking, prior myocardial infarction, or renal dysfunction,[24–27] and only modestly positively correlated with NT-proBNP.[25] In a systematic review, Janssen et al concluded that natriuretic peptides before LVAD implantation are not predictive of all-cause mortality.[28] On the other hand,

Table 3. JM Results for Time-Dependent sST2 and Survival and Right Heart Failure

	Survival		Right heart failure	
Variable	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age at implantation, y	0.99 (0.96–1.02)	0.58	1.00 (0.96–1.03)	0.83
Male sex	1.32 (0.59–3.07)	0.53	1.30 (0.43–4.29)	0.69
Ischemic cause	1.13 (0.46–2.89)	0.83	0.52 (0.11–1.90)	0.37
BMI, kg/m^2	1.06 (0.98–1.13)	0.11	0.97 (0.87–1.08)	0.57
RV function	0.78 (0.46–1.32)	0.36	1.18 (0.53–1.39)	0.71
INTERMACS score	1.02 (0.67–1.50)	0.92	0.52 (0.26–1.01)	0.06
Time-dependent sST2	1.20 (1.10–1.30)	<0.01	1.22 (1.07–1.39)	0.01

BMI indicates body mass index; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; JM, joint model; RV, right ventricular; and sST2, soluble suppression of tumorigenicity-2.

Bellavia et al showed that higher preoperative levels of NT-proBNP were associated with a higher risk of post-LVAD right heart failure.

Recently, some short-term studies on sST2 were performed in patients with end-stage heart failure on LVAD support.[9,26] In a prior pilot study, we reported sST2 analysis in 38 patients with end-stage heart failure both before and up until 6 months after LVAD implantation. sST2 was elevated in patients just before LVAD implantation and decreased to normal values within 3 to 6 months after primary LVAD surgery. No difference was observed between male and female patients.[9] In contrast, Denfeld et al found a different sST2 trajectory in 79 male and 19 female patients within the first 6 months after LVAD implantation, whereas fairly similar trajectories in symptoms were demonstrated from preimplantation to 6 months postimplantation. Female patients showed an initial increase after implantation, followed by a decrease, whereas male patients showed an overall decrease.[29] In the current study, none of the covariates, including sex, were independent predictors for adverse outcome in addition to longitudinal sST2 measurements.

Our study revealed no significant relation between the instantaneous slope of sST2 and either primary or secondary outcome. This is in line with the findings of Vark et al, who found no significant relationship between the instantaneous slope of sST2 and all-cause mortality and heart failure rehospitalization in patients with heart failure.[11] However, the relationship may be diminished because of the limited monitoring frequency or relatively low number of patients with increasing levels of sST2, which therefore might have led to an underestimation of the effect slope by the linear mixed model.

To the best of our knowledge, we were the first to evaluate the predictive value of serially measured sST2 in patients on long-term LVAD support after adjustment for NT-proBNP. For the current study, we used a JM approach, to allow for analysis with irregular and longitudinal sST2 measurements and different types of outcome. JM allows for individual variation, because of the use of a random effect for both the intercept and time in the linear mixed effect models.[15] In addition, it allows for evaluation of the effect of an instantaneous slope in the biomarker of interest in addition to the predicted instantaneous value at the time of the event (or end of the follow-up). To deal with the competing risks, we used 2 cause-specific Cox models in the JMs. The cause-specific hazard function indicates the hazard rate of an event in subjects who are currently free of events.[30] Within JM, we were also able to adjust for important covariates, including serially measured NT-proBNP.

Limitations

This study has some limitations. sST2 was not measured at fixed intervals in all patients from the start in 2015. Hence, the follow-up of some patients is relatively short, with a median follow-up of 25 months. In addition, sST2 measurements in some patients were irregular or absent. The LME model used to estimate the trajectory of sST2 may have overestimated or underestimated the actual sST2 measures, of which the direction is unknown. Preoperative sST2 levels were present in a relatively small subset of patients (86/237), including patients who were more stable at the time of implant, for INTERMACS score and RV function. So, patients with less severe disease were included for this analysis, which could have affected the results (eg, underestimation of the effect). Therefore, this cannot directly be extrapolated to the whole population with an LVAD. To deal with missing and irregular data, we used a JM approach that estimates the trajectory of postoperative sST2 levels. Because of the relatively low number of events, we were not able to distinguish predictive values specific for different types of cause of deaths. Possibly, the association between time-dependent sST2 and right heart failure after adjustment for serially measured NT-proBNP did not reach statistical significance because of a relatively small patient cohort. Most of the population was White race and therefore the results cannot be extrapolated to other races. Our analysis showed no significant difference in sST2 trajectories after HeartWare or HM3 implantation. However, this result needs to be replicated in a larger cohort to ensure adequate power with respect to conclusions on different types of LVAD support. Interdevice specifications cannot be addressed in the current study design, and differences in engineering and design of the devices may have influenced the results. In addition, the maximum number of covariates in the JM is related to sample size. Increasing patient numbers would allow for additional clinically relevant parameters, such as early postoperative heart rate or the diurnal pattern of sST2.[31,32] Last, the current study is hypothesis generating, as sST2 research in patients with end-stage heart failure on LVAD support is scarce. Additional studies are warranted before sST2 is recommended to be widely used as a predictive parameter in daily clinical routine for patients with an LVAD.

CONCLUSIONS

Now that the predictive role of sST2 both early and late after LVAD implantation has been established, the question becomes how often and at which moments sST2 should be measured. Because high-frequency monitoring results in high costs and patient burden, future research is warranted to define the optimal monitoring frequency. Repeated echocardiography and pump parameter evaluation are suggested for patients with persistently high sST2. In addition, it is

recommended to investigate whether sST2 responds to interventions such as heart failure medication or pump speed adjustment. Also, future studies with higher-frequency sST2 measurements in a larger patient cohort should define a cutoff value for patients with an LVAD, being a specific subgroup of patients with heart failure. The current study focused on repeatedly measured sST2 and identified it as a crucial biomarker, after adjustment for NT-proBNP, but prediction models can be enhanced in the future by adding other biomarkers or clinical and echocardiographic variables. Altogether, early interventions in patients with an LVAD with elevated sST2 levels may assist in preventing complications.

In conclusion, sST2 predicts all-cause mortality after LVAD implantation after adjustment for NT-proBNP. For right heart failure, this prediction was not significant after adjustment for NT-proBNP. The time-dependent level of postoperative sST2 is predictive, in contrast to the instantaneous change in sST2 at the time of the event or end of the follow-up. sST2 trajectories after LVAD implantation do not cluster per type of LVAD. A closer follow-up can be appropriate in patients with high sST2 levels. Further research is warranted into the optimal monitoring frequency, the mechanisms of elevated sST2 in patients with an LVAD, and possible targeted interventions.

ARTICLE INFORMATION

Received February 15, 2023; accepted November 1, 2023.

Affiliations

Department of Cardiology, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands (L.N., M.I.O., M.G.v.d.M., N.d.J., F.W.A., L.W.V.L.); Department of Methodology and Statistics, Utrecht University, Utrecht, the Netherlands (E.A.); Department of Cardiothoracic Surgery, University Medical Center Utrecht, University of Utrecht, Utrecht, the Netherlands (F.R., A-M.O.); Department of Central Diagnostic Laboratory, University Medical Center Utrecht, Utrecht, the Netherlands (H.K.); Institute of Cardiovascular Science, Faculty of Population Health Sciences (F.W.A.) and Health Data Research UK and Institute of Health Informatics (F.W.A.), University College London, London, United Kingdomand Department of Cardiology, Amsterdam Cardiovascular Sciences, Amsterdam University Medical Centre, University of Amsterdam, Amsterdam, the Netherlands (F.W.A.).

Sources of Funding

The collaboration project is cofunded by the public-private partnership allowance made available by Health-Holland, Top Sector Life Sciences and Health, to stimulate public-private partnerships (left ventricular assist devices provide loads of valuable additional data, LSHM19035).

Disclosures

Dr Van Laake received consultancy fees from Medtronic, Abbott Vifor, and Novartis, outside the submitted work. Dr Oerlemans received consultancy fees from Alnylam, Pfizer, Johnson & Johnson, and Novartis, paid to the University Medical Center Utrecht, outside the submitted work. The remaining authors have no disclosures to report.

Supplemental Material

Table S1
Figures S1–S5

REFERENCES

1. Bayes-Genis A, Zhang Y, Ky B. ST2 and patient prognosis in chronic heart failure. *Am J Cardiol*. 2015;115:64B–69B. doi: 10.1016/j.amjcard.2015.01.043
2. Veeraveedu PT, Sanada S, Okuda K, Fu HY, Matsuzaki T, Araki R, Yamato M, Yasuda K, Sakata Y, Yoshimoto T, et al. Ablation of IL-33 gene exacerbate myocardial remodeling in mice with heart failure induced by mechanical stress. *Biochem Pharmacol*. 2017;138:73–80. doi: 10.1016/j.bcp.2017.04.022
3. Mildner M, Storka A, Lichtenauer M, Mlitz V, Ghannadan M, Hoetzenecker K, Nickl S, Dome B, Tschachler E, Ankersmit HJ. Primary sources and immunological prerequisites for sST2 secretion in humans. *Cardiovasc Res*. 2010;87:769–777. doi: 10.1093/cvr/cvq104
4. Tseng CCS, Huibers MMH, van Kuik J, de Weger RA, Vink A, de Jonge N. The interleukin-33/ST2 pathway is expressed in the failing human heart and associated with pro-fibrotic remodeling of the myocardium. *J Cardiovasc Transl Res*. 2018;11:15–21. doi: 10.1007/s12265-017-9775-8
5. Aimo A, Januzzi JL, Bayes-Genis A, Vergaro G, Sciarrone P, Passino C, Emdin M. Clinical and prognostic significance of sST2 in heart failure: JACC review topic of the week. *J Am Coll Cardiol*. 2019;74:2193–2203. doi: 10.1016/j.jacc.2019.08.1039
6. Burkhoff D, Topkara VK, Sayer G, Uriel N. Reverse remodeling with left ventricular assist devices. *Circ Res*. 2021;128:1594–1612. doi: 10.1161/CIRCRESAHA.121.318160
7. Rame JE, Pagani FD, Kiernan MS, Oliveira GH, Birati EY, Atluri P, Gaffey A, Grandin EW, Myers SL, Collum C, et al. Evolution of late right heart failure with left ventricular assist devices and association with outcomes. *J Am Coll Cardiol*. 2021;78:2294–2308. doi: 10.1016/j.jacc.2021.09.1362
8. Potapov EV, Nersesian G, Lewin D, Özbaran M, de By TMMH, Stein J, Pya Y, Gummert J, Ramjankhan F, Zembala MO, et al. Propensity score-based analysis of long-term follow-up in patients supported with durable centrifugal left ventricular assist devices: the EUROMACS analysis. *Eur J Cardiothorac Surg*. 2021;60:579–587. doi: 10.1093/ejcts/ezab144
9. Tseng CCS, Huibers MMH, Gaykema LH, Siera-de Koning E, Ramjankhan FZ, Maisel AS, de Jonge N. Soluble ST2 in end-stage heart failure, before and after support with a left ventricular assist device. *Eur J Clin Investig*. 2018;48:1–5. doi: 10.1111/eci.12886
10. Opfermann P, Simader E, Felli A, Bevilacqua M, Holaubek C, Dworschak M, Mouhieddine M, Zimpfer D, Ankersmit JH, Steinlechner B. Early sST2 liberation after implantation of a left ventricular assist device in patients with advanced heart failure. *J Immunol Res*. 2020;2020:5826176–9. doi: 10.1155/2020/5826176
11. van Vark LC, Lesman-Leegte I, Baart SJ, Postmus D, Pinto YM, Orsel JG, Westenbrink BD, Brunner-la Rocca HP, van Miltenburg AJM, Boersma E, et al. Prognostic value of serial ST2 measurements in patients with acute heart failure. *J Am Coll Cardiol*. 2017;70:2378–2388. doi: 10.1016/j.jacc.2017.09.026
12. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007;370:1453–1457. doi: 10.1016/S0140-6736(07)61602-X
13. Dieplinger B, Egger M, Gegenhuber A, Haltmayer M, Mueller T. Analytical and clinical evaluation of a rapid quantitative lateral flow immunoassay for measurement of soluble ST2 in human plasma. *Clin Chim Acta*. 2015;451:310–315. doi: 10.1016/j.cca.2015.10.015
14. Emdin M, Aimo A, Vergaro G, Bayes-Genis A, Lupón J, Latini R, Meessen J, Anand IS, Cohn JN, Gravning J, et al. sST2 predicts outcome in chronic heart failure beyond NT–proBNP and high-sensitivity troponin T. *J Am Coll Cardiol*. 2018;72:2309–2320. doi: 10.1016/j.jacc.2018.08.2165
15. Rizopoulos D. The R package jmbayes for fitting joint models for longitudinal and time-to-event data using MCMC. *J Stat Softw*. 2016;72:1–42. doi: 10.18637/jss.v072.i07
16. Oemrawsingh RM, Akkerhuis KM, de Mulder M, Umans VA, Kietselaer B, Schotborgh C, Ronner E, Lenderink T, Liem A, Haitsma D, et al. High-frequency biomarker measurements of troponin, NT-proBNP, and C-reactive protein for prediction of new coronary events after acute coronary syndrome. *Circulation*. 2019;139:134–136. doi: 10.1161/CIRCULATIONAHA.118.036349

17. Hurst TE, Xanthopoulos A, Ehrlinger J, Rajeswaran J, Pande A, Thuita L, Smedira NG, Moazami N, Blackstone EH, Starling RC. Dynamic prediction of left ventricular assist device pump thrombosis based on lactate dehydrogenase trends. *ESC Heart Fail*. 2019;6:1005–1014. doi: 10.1002/ehf2.12473
18. Numan L, Ramjankhan FZ, Oberski DL, Oerlemans MIFJ, Aarts E, Gianoli M, Van Der Heijden JJ, DeJonge N, Van Der Kaaij NP, Meuwese CL, et al. Propensity score-based analysis of long-term outcome of patients on HeartWare and HeartMate 3 left ventricular assist device support. *ESC Heart Fail*. 2021;8:1596–1603. doi: 10.1002/ehf2.13267
19. Pagani FD, Cantor R, Cowger J, Goldstein DJ, Teuteberg JJ, Mahr CW, Atluri P, Kilic A, Maozami N, Habib RH, et al. Concordance of treatment effect: an analysis of the Society of thoracic surgeons intermacs database. *Ann Thorac Surg*. 2022;113:1172–1182. doi: 10.1016/j.athoracsur.2021.05.017
20. Wei P, Liu L, Wang X, Zong B, Liu X, Zhang M, Fu Q, Wang L, Cao B. Expression of soluble ST2 in patients with essential hypertension and its relationship with left ventricular hypertrophy. *ESC Heart Fail*. 2023;10:303–310. doi: 10.1002/ehf2.14147
21. Richards AM. N-terminal B-type natriuretic peptide in heart failure. *Heart Fail Clin*. 2018;14:27–39. doi: 10.1016/j.hfc.2017.08.004
22. Weinberg EO, Shimpo M, De Keulenaer GW, De MacGillivray C, Tominaga S, Solomon SD, Rouleau J, Lee RT. Expression and regulation of ST2, an Interleukin-1 receptor family member, in cardiomyocytes and myocardial infarction. *Circulation*. 2002;106:2961–2966. doi: 10.1161/01.CIR.0000038705.69871.D9
23. Lotierzo M, Dupuy AM, Kalmanovich E, Roubille F, Cristol JP. sST2 as a value-added biomarker in heart failure. *Clin Chim Acta*. 2020;501:120–130. doi: 10.1016/j.cca.2019.10.029
24. Wojtczak-Soska K, Pietrucha T, Sakowicz A, Lelonek M. Soluble ST2 protein in chronic heart failure is independent of traditional factors. *Arch Med Sci*. 2013;9:21–26. doi: 10.5114/aoms.2013.33344
25. Sabatine MS, Morrow DA, Higgins L, MacGillivray C, Bode C, Rifai N, Cannon CP, Gerszten RE, Lee RT. Complementary roles for biomarkers of biomechanical strain ST2 and N-terminal prohormone B-type natriuretic peptide in patients with ST-elevation myocardial infarction. *Circulation*. 2008;117:1936–1944. doi: 10.1161/CIRCULATIONAHA.107.728022
26. Bayes-Genis A, Zamora E, De Antonio M, Galán A, Vila J, Urrutia A, Díez C, Coll R, Altimir S, Lupón J. Soluble ST2 serum concentration and renal function in heart failure. *J Card Fail*. 2013;19:768–775. doi: 10.1016/j.cardfail.2013.09.005
27. Homsak E, Gruson D. Soluble ST2: a complex and diverse role in several diseases. *Clin Chim Acta*. 2020;507:75–87. doi: 10.1016/j.cca.2020.04.011
28. Janssen E, Jukema JW, Beeres SLMA, Schalij MJ, Tops LF. Prognostic value of natriuretic peptides for all-cause mortality, right ventricular failure, major adverse events, and myocardial recovery in advanced heart failure patients receiving a left ventricular assist device: a systematic review. *Front Cardiovasc Med*. 2021;8:699492. doi: 10.3389/fcvm.2021.699492
29. Denfeld QE, Faulkner KM, Davis MR, Habecker BA, Chien CV, Gelow JM, Mudd JO, Hiatt SO, Grady KL, Lee CS. Exploring gender differences in trajectories of clinical markers and symptoms after left ventricular assist device implantation. *Eur J Cardiovasc Nurs*. 2021;20:648–656. doi: 10.1093/eurjcn/zvab032
30. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. *Circulation*. 2016;133:601–609. doi: 10.1161/CIRCULATIONAHA.115.017719
31. Schlöglhofer T, Wittmann F, Paus R, Riebandt J, Schaefer AK, Angleitner P, Granegger M, Aigner P, Wiedemann D, Laufer G, et al. When nothing goes right: risk factors and biomarkers of right heart failure after left ventricular assist device implantation. *Lifestyles*. 2022;12:459. doi: 10.3390/life12030459
32. Crnko S, Printezi MI, Jansen TPJ, Leiteris L, van der Meer MG, Schutte H, van Faassen M, du Pré BC, de Jonge N, Asselbergs FW, et al. Prognostic biomarker soluble ST2 exhibits diurnal variation in chronic heart failure patients. *ESC Heart Fail*. 2020;7:1224–1233. doi: 10.1002/ehf2.12673