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ORIGINAL ARTICLE

Persistently elevated levels of sST2 after acute coronary syndrome are associated with recurrent cardiac events

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ABSTRACT

Purpose: Higher soluble ST2 (sST2) levels at admission are associated with adverse outcome in acute coronary syndrome (ACS) patients. We studied the dynamics of sST2 over time in post-ACS patients prior to a recurrent ACS or cardiac death.

Methods: We used the BIOMArCS case cohort, consisting of 187 patients who underwent serial blood sampling during one-year follow-up post-ACS. sST2 was batch-wise quantified after completion of follow-up in a median of 8 (IQR: 5–11) samples per patient. Joint modelling was used to investigate the association between longitudinally measured sST2 and the endpoint, adjusted for gender, GRACE risk score and history of cardiovascular diseases.

Results: Median age was 64 years and 79% were men. The 36 endpoint patients had systematically higher sST2 levels than those that remained endpoint free (mean value 29.6 ng/ml versus 33.7 ng/ml, p-value 0.052). The adjusted hazard ratio for the endpoint per standard deviation increase of sST2 was 1.64 (95% confidence interval: 1.09–2.34; $p = 0.019$) at any time point. We could not identify a steady or sudden increase of sST2 in the run-up to the combined endpoint.

Conclusion: Asymptomatic post-ACS patients with persistently higher sST2 levels are at higher risk of recurrent ACS or cardiac death during one-year follow-up.

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sST2; secondary prevention; repeated measurements; acute coronary syndrome; atherosclerosis

Introduction

ST2 is a promising biomarker in cardiovascular disease. ST2 is an interleukin (IL) 1 receptor that binds to its ligand IL-33 (Schmitz *et al.* 2005, Altara *et al.* 2018). There are two types of ST2: soluble ST2 (sST2), which is a circulation biomarker that can be identified and quantified by assays, and: membrane-bound ST2L (ST2 gene-like). In response to cardiac stress, the IL-33/ST2L interaction is upregulated to induce protective inflammatory pathways reducing adverse cardiomyocyte remodelling. However, sST2 acts as a decoy receptor for circulating IL-33, hereby preventing and regulating ST2L stimulation by IL-33 (Schmitz *et al.* 2005, Pascual-Figal and Januzzi 2015, Altara *et al.* 2018).

sST2 concentrations have been extensively investigated in heart failure patients and it has been shown that elevated concentrations are strongly correlated with adverse outcomes. Therefore, measuring sST2 for prognostication is now advocated in heart failure guidelines (Yancy et al. 2017). Conversely, the role of sST2 in the progression of atherosclerosis is less clear. It has been proposed that the IL-33/ST2L interaction in the coronary arterial wall may direct the immune response to limiting plaque inflammation and evolution. Again, sST2 would prevent the circulating IL-33 from binding to ST2L and therefore result in more inflammation and plaque progression (Aimo *et al.* 2018). However, studies investigating the association of sST2 with atherosclerosis and atherosclerotic events are scarce and provide conflicting results (Dhillon *et al.*, 2011, 2013, Dieplinger *et al.* 2014, O'Malley *et al.* 2014, Oh *et al.* 2016). Where some studies did find a significant association between sST2 and clinical endpoints, others were not able to do so. In addition, so far only baseline sST2 measurements have been used to study the association with clinical endpoints.

In the current study, we investigated the dynamics of sST2 using repeated blood sampling over a one-year follow-up in patients admitted for acute coronary syndrome (ACS) and correlated these dynamics with the occurrence of reACS or cardiac death. More particularly, we investigated if high-frequency post-discharge sST2 measurements over time may

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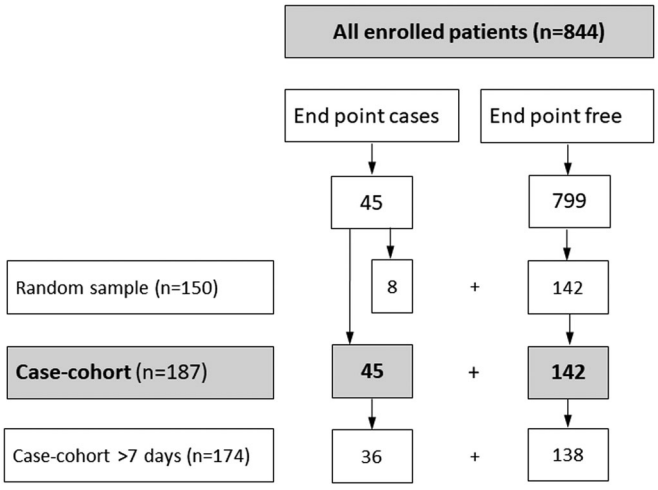

Figure 1. Patient flow chart case-cohort. First, a *random* sample of 150 patients of our full cohort (844) was selected which rendered 8 endpoint cases, which was then complemented with all endpoint cases outside the random sample. Consequently, the case-cohort sample included all 45 study endpoint cases and 142 endpoint-free patients. 7 days post the index event, blood samples were available of 174 patients.

detect episodes of increased coronary vulnerability in ACS patients. If such periods could be identified, clinicians could use this information for further diagnostics and potentially perform preventive interventions.

Clinical significance

- In the current study, we investigated the dynamics of sST2 using repeated blood sampling over a one-year follow-up in patients admitted for ACS and correlated these dynamics with the occurrence of reACS or cardiac death.
- Post-ACS patients with persistently elevated sST2 concentrations are at higher risk of reACS or cardiac death during one year for follow-up.
- Using repeated ST2 measurements did not lead to a statistically significantly better prediction of the endpoint than using a single measurement taken at least seven days after the index-ACS.

Methods

Study design

The design, sample size calculation, statistical considerations and other details of the BIOMarker study to identify the Acute risk of a Coronary Syndrome (BIOMArCS) have been extensively described in previous papers (Oemrawsingh *et al.* 2016, 2019). In short, BIOMArCS is a multicentre (18 hospitals in the Netherlands) prospective study designed to study biomarker evolutions using high-frequency blood sampling during one year of follow-up after admission for ACS. It included patients aged 40 years or older admitted with an ACS in combination with at least one additional cardiovascular risk factor. Exclusion criteria were ischaemia precipitated by a condition other than atherosclerotic CAD, a left ventricular ejection fraction $<30\%$, or end-stage congestive heart failure (NYHA class $>=$ 3), severe chronic kidney disease, or a coexistent condition with life expectancy <1 year. The study endpoint was a combination of cardiac death, myocardial infarction, and unstable angina requiring urgent coronary revascularization, and was eventually reached by 45 patients. All patients were treated according to prevailing guidelines and at the discretion of the treating physician. The study protocol was approved by the Institutional Review Board of the participating hospitals, and all study subjects gave written informed consent.

sST2 measurements

During follow-up patients underwent venepuncture at regular intervals: every two weeks during the first six months of follow-up and monthly thereafter. A patient's venepuncture schedule was discontinued after coronary artery bypass grafting, a hospital admission for heart failure or in case of a (sudden) decline in renal function to a glomerular filtration rate (eGFR) <30mL/min/1.73m^2, to avoid biased biomarker levels. On-site obtained blood samples were stored at -80 degrees Celsius after sample preparation within 82 (25th–75th percentile 58–117) minutes post withdrawal. Subsequently, all samples were securely transported to the Erasmus MC for long-term storage. Serum samples were used to batch-wise quantify sST2 levels (Presage ST2 assay, Critical diagnostics, San Diego, CA, USA), blinded for patient characteristics and outcome. The lower limit of detection was 1.31 ng/ml with reference values of 8.5–49.3 ng/ml for man and 7.1–33.5 ng/ml for women; the analytical coefficient of variation was $<5\%$.

Case-cohort

We performed a case-cohort analysis within BIOMArCS. Motivation and details of the selection methods are extensively described elsewhere (Boersma *et al.* 2019). Briefly, from the full BIOMArCS cohort consisting of 844 patients, we *randomly* selected 150 patients (containing 8 study endpoint cases), and added the 37 study endpoint cases that were outside this random selection. Hence, the analysis dataset consisted of all 45 endpoint cases and 142 event-free patients. The study endpoint consisted of repeat ACS or cardiovascular death. All samples 7 days post the index ACS were included, to ensure that the direct effect of the index ACS on the sST2 levels has washed out (flow-chart is shown in Figure 1.) (Van Den Berg *et al.* 2020). For the remaining 174 patients (36 endpoint cases), a median of 8 (25th–75th percentile 5–11) serial samples were available, comprising 1282 samples altogether.

Statistical analysis

Continuous variables are presented as mean (standard deviation; SD) or median (25th–75th percentile), depending on their distributions. Categorical variables are summarised as numbers and percentages. We investigated the association between baseline measurements and the repeatedly measured ST2 concentration using linear mixed effects (LME)

models. In this model, ST2 was entered as the dependent variable, whereas the baseline characteristics of interest were entered as independent variables.

For investigating the predictive value of repeated sST2 measurements in ACS-patients, we used the framework of joint models for longitudinal and survival data (Rizopoulos 2016a). Within these joint models, the mixed effect model is used to model the biomarker trajectory for each individual patients which is than related in the Cox model with the time-to-event data. The result of the joint-model is presented as an adjusted hazard ratio (aHR) with 95% confidence interval per standard deviation increase in sST2 level on the log-scale.

Analyses were first performed univariable, and subsequently multivariable adjustment was performed. For this purpose, the GRACE risk score for assessment of post-discharge death and myocardial infarction, as recommended by international guidelines (Members *et al.* 2011, 2012, Amsterdam et al. 2014), was used. This specific GRACE risk model consists of age, troponin (or CKMB) elevation at admission, history of MI, congestive heart failure and whether CABG was performed at the index hospitalisation (Coordinating Center for the Global Registry of Acute Coronary Events CfOR 2016). The survival model was adjusted for the GRACE risk score, and the LME model was adjusted for GRACE risk score, sex, diabetes, history of coronary artery bypass surgery, history of valvular heart disease, and history of peripheral arterial disease.

Analyses were performed with R Statistical Software, in particular the packages *nlme* and *JMbayes* (Pinheiro *et al.*, 2014, Rizopoulos 2016b). Statistical tests were two-tailed and a *p*-value of 0.05 was used as threshold of statistical significance.

Results

Baseline characteristics of sST2

The median age of all patients was 64 years (25th–75th percentile 55.3–71.6), and 79% were men. Patients had a CCS Angina Grading Scale $\leq$1 at 95% of the sample moments and a NYHA classification $\leq$1 at 93% of the sample moments, reflecting clinical stability. The average eGFR per patient, calculated using all sample moments, was 90.9 (25th–75th percentile 72.4–111.4) mL/min/1.73m^2. Clinical characteristics of the endpoint cases versus the endpoint-free patients are described in Table 1. The prevalence of diabetes mellitus, history of coronary bypass grafting and peripheral artery disease was higher in endpoint cases. In addition, these patients had a significant higher GRACE risk score (121 [IQR 98–141] points versus 109 [IQR 88–130] points) corresponding to a difference in probability of post-discharge death or myocardial infarction of 6% versus 4%. To see if sST2 levels differ per baseline characteristic, Table 2 shows the association of linear sST2 level with baseline characteristics. Patients with peripheral vessel disease clearly had higher concentrations than patients without peripheral vessel disease.

Recurrent cardiac events and sST2

During one year of follow-up post ACS, cases had on average higher sST2 level than non-cases (29.6 ng/ml versus 33.7 ng/ml, *p*-value 0.052). The adjusted HR for the endpoint per standard deviation increase was 1.64 (95% confidence interval: 1.09-2.34; $p = 0.019$) at any time point. To ease the interpretation of this adjusted HR, we have back transformed the mean and the -/+1SD levels of the log ST2: mean ST2: 29.9 ng/ml, −1 SD: 21.3 ng/ml, +1 SD: 42 ng/ml.

We could not identify a steady or sudden increase of sST2 in the run-up to the study endpoint (Figure 2). Repeatedly measured serum levels resulted in slightly improved discrimination between cases and non-cases compared to a randomly selected *single* measurement taken during the stable phase of the follow-up, but this difference did not reach statistical significance (C-index 0.59 vs 0.57, $p = 0.53$).

Discussion

Our research has shown that post-ACS patients with persistently elevated sST2 concentrations are at higher risk of fatal or non-fatal reACS during one year of follow-up. Although the average sST2 concentrations during follow-up in our post-ACS population were relatively low, patients with persistently higher sST2 concentrations had an increased risk to develop reACS or cardiac death at any time point during follow-up. No significant increase of sST2 concentrations was found prior to an event. Consequently, using repeated ST2 measurements did not lead to a statistically significantly better prediction of the endpoint than using a single measurement taken at least seven days after the index-ACS.

It is difficult to compare our results to previously published papers associating sST2 in an ACS populations to coronary events as the studies differ in critical aspects of design, endpoints and used sST2 panels. In a recent meta-analysis investigating the association between sST2 and long-term prognosis of patients with coronary artery disease, higher baseline sST2 concentrations were associated with higher risk of major adverse cardiac events, all-cause mortality, cardiovascular death and heart failure but not to myocardial infarction (Liu *et al.* 2020). There were only two studies included in the meta-analysis associating sST2 with myocardial infarction, which showed conflicting results (Dhillon *et al.* 2011, 2013). Examining the studies in more detail, both studies were performed by Dhillon et al and had comparable study designs. The first study included 677 STEMI patients (Dhillon *et al.* 2013) and the second study included 577 NSTEMI patients (Dhillon *et al.* 2011). In both studies, sST2 concentrations were measured between day 3 and 5 prior to discharge and patient follow-up was approximately one year. Surprisingly, in both studies, the authors chose to log10-transform the sST2 concentrations and therefore hazard ratios refer to a 10-fold change in concentration. The authors found no association between sST2 and re-infarction in STEMI-patients but did find that a 10-fold increase of sST2 levels was associated with a 2.5 times higher risk of re-infarction in NSTEMI-patients. In both studies, sST2 concentrations

Table 1. Patient characteristics of the case-cohort.

	Endpoint cases	Endpoint-free patients	*p* Value
Number of patients	45	142	
Age, yr (IQR)	67.4 (57.1-76.5)	62.6 (55.0-70.9)	0.075
Man, n (%)	36 (80.0)	111 (78.2)	0.79
Cardiovascular risk factors, n (%)			
Diabetes Mellitus	17 (37.8)	24 (16.9)	0.003
Hypertension	22 (48.9)	77 (54.2)	0.53
Hypercholesterolemia	20 (44.4)	72 (50.7)	0.46
Current smoker	17 (37.8)	60 (42.2)	0.52
History of cardiovascular disease, n (%)			
Myocardial infarction	14 (31.1)	43 (30.3)	0.92
Coronary artery bypass grafting	11 (24.4)	12 (8.5)	0.004
PCI	14 (31.1)	38 (27.0)	0.59
Stroke	9 (20.0)	16 (11.3)	0.13
Peripheral vessel disease	10 (22.2)	9 (6.3)	0.004
Admission diagnosis, n (%)			
STEMI	16 (35.6)	65 (45.8)	0.46
NSTEMI	22 (48.9)	56 (39.4)	
Unstable angina pectoris	7 (15.6)	21 (14.8)	
PCI performed	34 (87.2)	109 (82.6)	0.50
Physical examination			
GRACE risk score (IQR)	121 (98-141)	109 (88-130)	0.022
BMI (SD)	27.2 (3.7)	27.8 (3.8)	0.36
Heart rate (SD)	75 (16)	73 (17)	0.59
SBP (SD)	145 (24)	138 (27)	0.095
DBP (SD)	72 (3)	81 (17)	0.48
Discharge medication, n (%)			
Aspirin	45 (100)	132 (93.0)	0.20
P2Y12 inhibitor	44 (96.8)	128 (90.4)	0.37
Vitamin K antagonist	5 (9.7)	11 (7.9)	0.57
Statin	44 (96.8)	136 (95.6)	0.46
Beta-blocker	42 (93.5)	121 (85.1)	0.72
Ace inhibitor or ARB	41 (90.3)	120 (84.2)	1.00

Normally distributed continuous variables are presented as mean with SD, non-normally distributed continuous variables are presented as median with IQR. Categorical variables are presented as numbers and percentages.
ACE: angiotensin converting enzyme; ARB: angiotensin II receptor blocker; BMI: body mass index; CAD: coronary artery disease; DBP: diastolic blood pressure; GRACE risk score: Global Registry of Acute Coronary Events risk score; NSTEMI: non-STEMI; PCI: Percutaneous coronary intervention; SBP: systolic blood pressure; STEMI: ST-elevation myocardial infarction; yr: year.

Table 2. Association of sST2 with baseline characteristics.

	Estimate (95% confidence interval)	*p* Value
Man	5.61 (−2.17, 13.39)	0.16
Body mass index	0.30 (−0.58, 1.18)	0.50
Age (years)	0.23 (−0.06, 0.57)	0.11
Cardiovascular risk factor		
Diabetes	0.79 (−6.94, 8.52)	0.84
Hypertension	3.53 (−2.90, 9.96)	0.28
Hypercholesterolemia	−1.58 (−7.84, 4.68)	0.62
Active smoking	−2.84 (−9.34, 3.66)	0.39
Serum creatinine (μmol/L)	−0.022 (−0.18, 0.13)	0.78
History of cardiac disease		
Myocardial infarction	−4.42 (−12.97, 4.14)	0.31
Coronary artery bypass grafting	−0.16 (−10.95, 10.63)	0.98
Percutaneous coronary intervention	1.96 (−6.40, 10.33)	0.64
Stroke	−1.86 (−11.99, 8.27)	0.72
Periferal vessel disease	11.91 (1.16, 22.67)	0.030

Estimates from linear mixed model with sST2 as dependent variable and baseline characteristics as independent variables. The estimates depict the rise in average sST2 levels during follow-up.

were associated with death, but unfortunately analyses with the combined endpoint re-infarction and death were lacking. In addition to these two studies, we found another study not included in the meta-analysis reporting the relation between sST2 and myocardial infarction. In this study, baseline sST2 concentrations were measured at day of admission in 4432 non-ST-elevation ACS patients. During a one-year follow-up, baseline sST2 concentrations were not significantly associated with the combined endpoint of re-infarction and cardiovascular death (O'Malley *et al.* 2014). Our study clearly distinguishes in design from the earlier described studies, linking sST2 concentrations to adverse events in ACS patients. Instead of measuring a single sample close to the initial index event, we repeatedly measured sST2 in patients >7 days post-ACS. We purposely chose to discard the measurements from the first 7 days as it has been shown by Van den Berg et al that sST2 levels are increased directly after an ACS and it takes on average a week before stabilisation (Van Den Berg *et al.* 2020). In fact, serum sST2 levels taken within 24 hours of event have been associated with the extend of

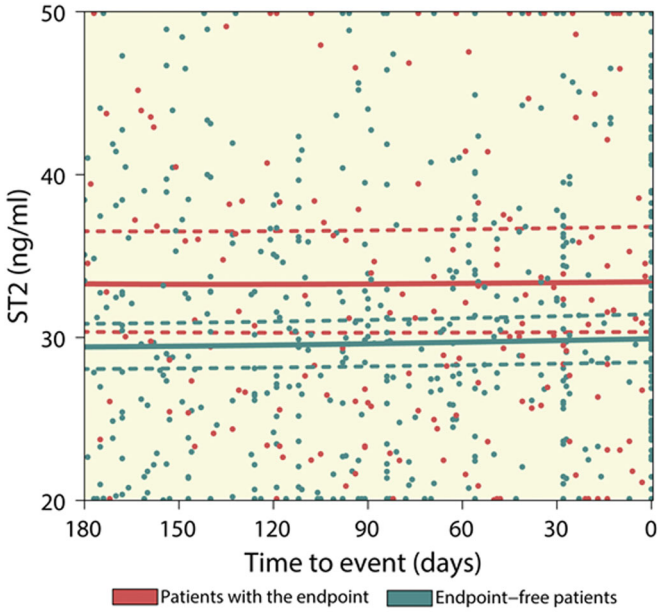

Figure 2. Average sST2 levels. The X-axis depicts time *until* event. Hence, day zero is the time of event or censoring. The thick line shows the average value of sST2 in either patients in whom the endpoint occurred (red), or endpoint-free patients (green). 1282 samples were used for printed analysis results. sST2: soluble Suppression of Tumorigenicity-2; ng/ml: Nano grams per millilitre.

remodelling caused by an ACS (Minana *et al.* 2018), which is a risk factor for future adverse cardiac outcome by itself. Moreover, we included all ACS patients and not solely NSTEMI or STEMI patients. Finally, our study used the combined endpoint of fatal or non-fatal ACS. Since myocardial infarction may cause cardiac death, censoring for cardiac death to obtain the single endpoint myocardial infarction leads to uninformative censoring. These patients will be censored although they have developed myocardial infarction. Hence using myocardial infarction as a single endpoint leads to a biased estimate.

Since sST2 level did not increase prior to an event, sST2 may not be a marker of acute plaque progression causing thromboembolic events. However, our study did show that sST2 level is independently associated with recurrent ACS and cardiac death. In addition, sST2 has showed to be a stable marker over time. As previously described, higher sST2 levels may increase inflammation and plaque progression since sST2 acts as a decoy receptor of IL-33. Hence, it seems that higher sST2 level might be a marker of high-risk atherosclerotic disease. Future studies should asses if a single random sST2 concentration taken at least one week after the index event could add prognostic value next to other established biomarkers, preferably in a multimarker approach.

Limitations

So far, the dynamics of sST2 using repeated measurements after an ACS and prior to a recurrent ACS had not yet been investigated. Our study is distinctive in that we obtained a large number (median 8 per patient) of repeated measurements to provide a detailed description of the temporal evolution of sST2 in individuals during the first year after ACS admission. As such, our findings are accurate and robust. However, our study was limited with respect to the number of patients who reached the study endpoint. Hence, we were unable to adjust the observed relation between sST2 and recurrent ACS for other prognostic markers and for residual confounders.

Conclusion

In conclusion, asymptomatic post-ACS patients with persistently higher sST2 levels are at increased risk of recurrent ACS or cardiac death. However, sST2 cannot be used to predict the timing of an adverse event. The role of sST2 for risk prediction in patients with clinically stable CAD warrants further investigation.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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References

Aimo, A., *et al.*, 2018. The IL-33/ST2 pathway, inflammation and atherosclerosis: trigger and target? *International journal of cardiology*, 267, 188–192.

Altara, R., *et al.*, 2018. Conflicting vascular and metabolic impact of the IL-33/sST2 axis. *Cardiovascular research*, 114 (12), 1578–1594.

Amsterdam, E.A., *et al.*, 2014. AHA/ACC guideline for the management of patients with non–ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Journal of the American college of cardiology*, 64 (24), e139–e228.,

Boersma, E., *et al.*, 2019. Details on high frequency blood collection, data analysis, available material and patient characteristics in BIOMArCS. *Data in brief*, 27, 104750.

Coordinating Center for the Global Registry of Acute Coronary Events Cfor. 2016. Methods and formulas used to calculate the GRACE Risk Scores for patients presenting to hospital with an acute coronary syndrome. https://www.outcomes-umassmed.org/grace/files/GRACE_RiskModel_Coefficients.pdf

Dhillon, O.S., *et al.*, 2013. Pre-discharge risk stratification in unselected STEMI: is there a role for ST2 or its natural ligand IL-33 when compared with contemporary risk markers? *International journal of cardiology*, 167 (5), 2182–2188.

Dhillon, O.S., *et al.*, 2011. Interleukin 33 and ST2 in non–ST-elevation myocardial infarction: comparison with global registry of acute coronary events risk scoring and NT-proBNP. *American heart journal*, 161 (6), 1163–1170.

Dieplinger, B., *et al.*, 2014. Increased soluble ST2 predicts long-term mortality in patients with stable coronary artery disease: results from the Ludwigshafen risk and cardiovascular health study. *Clinical chemistry*, 60 (3), 530–540.

Liu, N., *et al.*, 2020. The association between soluble suppression of tumorigenicity-2 and long-term prognosis in patients with coronary artery disease: A meta-analysis. *PLoS one*, 15 (9), e0238775.

Members, A.T.F., *et al.*, 2011. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute

coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC.). *European heart journal*, 32, 2999–3054.

Steg, P.G., *et al*.,; Authors/Task Force Members. 2012. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). *European heart journal*, 33 (20), 2569–2619.,

Minana, G., *et al*., 2018. ST2 and left ventricular remodeling after ST-segment elevation myocardial infarction: a cardiac magnetic resonance study. *International journal of cardiology*, 270, 336–342.

O'malley, R.G., *et al*., 2014. Prognostic performance of multiple biomarkers in patients with non-ST-segment elevation acute coronary syndrome: analysis from the MERLIN-TIMI 36 trial (Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes-Thrombolysis In Myocardial Infarction 36.). *Journal of the American college of cardiology*., 63, 1644–1653.

Oemrawsingh, R.M., BIOMArCS Investigators., *et al*., 2019. High-frequency biomarker measurements of troponin, NT-proBNP, and C-reactive protein for prediction of new coronary events after acute coronary syndrome. *Circulation*, 139 (1), 134–136.

Oemrawsingh, R.M., *et al*., 2016. Cohort profile of BIOMArCS: the BIOMarker study to identify the Acute risk of a Coronary Syndrome-a prospective multicentre biomarker study conducted in the Netherlands. *BMJ open*, 6 (12), e012929.

Oh, J., *et al*., 2016. Lack of superiority for soluble ST2 over high sensitive C-reactive protein in predicting high risk coronary artery calcium score in a community cohort. *Yonsei medical journal*, 57 (6), 1347–1353.

Pascual-Figal, D.A., and Januzzi, J.L., 2015. The biology of ST2: the international ST2 consensus panel. *The american journal of cardiology*, 115 (7 Suppl), 3B–7B.

Pinheiro, J., Bates, D., Debroy, S. & Sarkar, D., 2014. R Core Team (2014) nlme: linear and nonlinear mixed effects models. R package version 3.1–117. Available at http://CRAN.R-project.org/package=nlme.

Rizopoulos, D., 2016a. The R Package JMbayes for fitting joint models for longitudinal and time-to-event data using MCMC. *Journal of Statistical Software*, 72, 46.

Rizopoulos, D., 2016b. The R Package JMbayes for Fitting Joint Models for Longitudinal and Time-to-Event Data Using MCMC. *Journal of statistical software*, 72 (7), 1–46.

Schmitz, J., *et al*., 2005. IL-33, an interleukin-1-like cytokine that signals via the IL-1 receptor-related protein ST2 and induces T helper type 2-associated cytokines. *Immunity*, 23 (5), 479–490.

Van Den Berg, V.J., BIOMArCS investigators., *et al*., 2020. Stabilization patterns and variability of hs-CRP, NT-proBNP and ST2 during 1 year after acute coronary syndrome admission: results of the BIOMArCS study. *Clinical chemistry and laboratory medicine*, 58 (12), 2099–2106.

Yancy, C.W., *et al*., 2017. ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Journal of the American college of cardiology*, 70 (6), 776–803.