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Heart Failure Therapy Induced Early ST2 Changes May Offer Long-term Therapy Guidance

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Conflict of interest

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Abstract

Background: Biomarkers may help to monitor and tailor treatment in patients with acute heart failure (AHF).

Methods: Levels of ST2, a novel biomarker integrating hypervolemic cardiac strain and proinflammatory signals, were measured at presentation to the emergency department (ED) and after 48 hours in 207 patients with AHF. Patients were stratified according to their early ST2 response (responders: ST2 decrease ≥25%; non-responders: ST2 decrease < 25%) and beta-blocker, RAAS blockade or diuretic treatment status at hospital discharge. We assessed the utility of ST2 levels and its changes to predict long-term mortality and the interaction between ST2 levels, treatment at discharge and one-year mortality.

Results: ST2 levels were higher in decedents than in survivors (median 108 vs. 69 ng mL^{-1}, $p<0.01$) and decreased significantly during the first 48 hours (median decrease 33%). ST2 decrease was less in decedents compared to survivors (median change: -25% versus -42%, $p<0.01$). In Cox regression early ST2 changes independently predicted one-year mortality (HR 1.07 for every increase of 10%; $p=0.02$).

RAAS blockers at discharge were associated with survival independent of ST2 response, whereas the association of beta-blockers with survival differed markedly according to ST2 response with beneficial effects restricted to ST2 non-responders (p for interaction=0.04). A similar albeit non-significant trend was observed for diuretics (p for interaction =0.11).

Conclusion: ED and serial ST2 measurements are independent predictors of one-year mortality in AHF.

Introduction

Acute heart failure (AHF) is a major medical and socioeconomic burden representing the most common discharge diagnosis in patients over 65 years of age (1). Additionally it has a poor prognosis; the 60 to 90 day mortality rate after discharge approaches 10% and almost half of all patients will be re-hospitalised within the first year (2). These alarming figures are further complicated by an ever aging, highly comorbid patient population (3) in whom cardiovascular polypharmacy is associated with considerable challenges and increased adverse events (4). Hence, a rapid and reliable predictor of treatment response to individual cardiovascular drug classes might aid physicians in tailoring therapy to the individual patient to maximize treatment success while minimizing unnecessary adverse events. This appears especially important, since in contrast to the stable chronic heart failure setting, none of the drugs currently used at ED presentation, during in-hospital treatment, or at hospital discharge have been shown to improve outcome when used in the AHF setting (2).

The use of cardiac biomarkers might be helpful to overcome at least some of the current limitations and individualize treatment (5-8). Suppression of tumorigenicity 2 (ST2) is a member of an interleukin-1 receptor family and consists of both a transmembrane receptor form (ST2L) and a truncated, soluble receptor form (ST2) that can be detected in serum. Its gene is seen to be upregulated in cardiac myocytes and fibroblasts subjected to mechanical stress such as cardiomycyte stretch (9). Additionally, both ST2 isoforms are tightly connected to the inflammatory cytokine network and subsequent repair mechanisms (10). Hence elevated ST2 levels integrate hypervolemic cardiac strain and proinflammatory activity signals. Importantly, the therapeutic effects of diuretic and beta-blocker therapy seem to be linked to volume-depletion (11) and anti-inflammatory modulation (12-14). Importantly, in an international multicentre study, enrolling 1059 patients ST2 levels were shown to have

greater short-term prognostic value than the two natriuretic peptides (BNP and NT-proBNP) for short-term mortality at 30 days (15).

We therefore assessed the utility of ST2 levels and its changes to predict on long-term mortality and evaluated the interaction between ST2 levels, treatment at hospital discharge and one-year mortality.

Methods

Setting and study population

We included 207 consecutive AHF patients presenting to the emergency department of the University Hospital Basel, Switzerland from April 2006 to August 2009. To be eligible for enrolment, patients had to be over 18 years old and present with symptoms and signs of AHF. AHF was diagnosed and patients were treated for AHF according to the current ESC guidelines (2). Patients undergoing chronic hemodialysis were excluded. The study was carried out according to the principles of the Declaration of Helsinki. It was approved by the local ethical committee. Written informed consent was obtained from all participants.

Clinical Evaluation

All patients underwent an initial clinical assessment that included a clinical history taking, a physical examination, electrocardiogram (ECG), continuous ECG monitoring, pulse oximetry, standard blood measurements including B-type natriuretic peptide (BNP) and chest radiography. Echocardiography was performed according to the treating physician. Left ventricular systolic dysfunction was defined as a left ventricular ejection fraction (LVEF) of 40% or less (2).

An adjudicated diagnosis of acute AHF was made by two independent cardiologists, who were blinded to the biomarker results, after reviewing all medical records pertaining to the individual patient (including results of standard investigations, the response to therapy, and autopsy data in those patients dying in-hospital). In situations of diagnostic disagreement, cases were reviewed and adjudicated in conjunction with a third cardiologist. The reviewing cardiologist and the authors were not directly involved in the clinical care of the study patients.

Biomarker measurements

Blood samples for determination of ST2 were collected at presentation and after 48 hours. After centrifugation, samples were frozen at −80℃ until assayed in a blinded fashion in a single batch using a monoclonal sandwich ELISA (Presage^{TM} ST2, Critical Diagnostics; San Diego, CA, USA). All frozen specimens were collected specifically for the purpose of analysing the potential value of novel biomarkers such as ST2 in monitoring and tailoring treatment in AHF. The lower detection limit of the assay is 2 U/ml, the upper detection limit is 200 U/ml (16). The within-run and total coefficients of variation are <2.5% and <4%. The limit of quantification is 3.3U/ml. The analyte is stable for 48h at room temperature, for 7 days at 4℃ and for at least 2 months at -20 and -80℃. The reference change value for healthy i ndividuals is 30% (17). (Reference change value describes the maximal change of a marker that can potentially be attributed to pre-analytical variation, analytical imprecision and biological variation.) Age-independent reference values in a biomarker-selected healthy cohort were 3-28 U mL^{-1} in men and 2-16 mL^{-1} in women (16).

Endpoints

The potential of ST2 ED measurements and 48h ST2 changes to predict mortality were assessed as primary endpoints. The impact of treatment at hospital discharge on one-year mortality according to ST2 strata was the secondary endpoint. Mortality was prospectively assessed during follow-up. Patients were contacted by telephone every 6 months after the initial presentation. In addition, referring physicians and administrative databases of the respective hometowns were contacted in case of uncertainties regarding health status or further hospitalizations. Twelve month survival status could be confirmed in all patients using this methodology.

Statistical analysis

The statistical analyses were performed using SPSS/PC version 19.0 (SPSS Inc., USA). A statistical significance level of <0.05 was used. Discrete variables are

expressed as counts (percentage) and continuous variables as means ± standard deviation (SD) or median and interquartile range [IR], unless stated otherwise. The comparison between survivors and decedents was done using chi-square test and Fisher exact test for categorical variables and t-test for continuous variables if normally distributed or Mann-Whitney test if not normally distributed. The Spearman rank correlation was used to perform correlation analyses. All hypothesis testing was two-tailed. Cox regression analysis was used to demonstrate prognostic independence of early ST2 changes from other prognostic factors. Receiver operating characteristic (ROC) curves were utilized to evaluate the accuracy of ST2, early ST2 changes and a clinical risk prediction model based on the ADHERE registry to predict death (18). In an analysis of 52 164 AHF patient-records Fonarow et al found high admission levels of blood urea nitrogen, low admission systolic blood pressure and high levels of serum creatinine to be the three best predictors of mortality (18). A clinical risk prediction model, based on these three parameters and the heart failure marker BNP, was used as a baseline model. Differences of areas under the ROC curve were evaluated with the method of DeLong et al. (19). Additionally, integrated discrimination improvement (IDI) analysis was assessed as a method to quantify the differences in the probabilities for events and nonevents based on the addition of ST2 and early ST2 changes to the baseline model (20). Kaplan-Meier cumulative survival curves were compared by the log-rank test.

Results

Baseline clinical and laboratory characteristics of study patients

Table 1 depicts baseline clinical and biochemical characteristics of the study population. The patient cohort was elderly with a median age of 80 years and 43% of all patients were women. At presentation the median BNP level was 1355pg/ml and the median echocardiographic LVEF was 40%. Median follow-up time was 368 days (range: 1-1333 days).

ST2 levels in AHF

ST2 values at presentation were significantly correlated to age (r= 0.19, p=0.046), eGFR (r= -0.20, p=0.027), C-reactive protein values (r= 0.42, p=<0.001), serum troponin T (r=0.40, p=<0.001) and leukocyte count (r= 0.35, p=<0.001) but not to B-type natriuretic peptide levels (r= 0.16, p=0.085) and hemoglobin levels (r= -0.05, p=0.569). The median ST2 value of the overall study population at presentation was 78 ng mL^{-1} (IQR: 46 - 121).

ST2 levels and short-term survival status

Overall, 16 (8%) patients died during the index hospitalization. There was no significant difference in age (p=0.24), systolic blood pressure (p=0.06), heart rate (0.28), and NYHA dyspnea class (0.17) between patients dying in-hospital and in-hospital survivors. ST2 levels at presentation were significantly higher in patients dying in-hospital (150.0 ng mL^{-1} 90.8-250.4 vs. 73.2 ng mL^{-1}43.2-113.9, p<0.01). However, there was no correlation between increasing ST2 levels and the duration of the in-hospital stay (p=0.62).

To assess the potential of ED measurements of ST2 to predict in-hospital mortality a receiver operating characteristics curve was drawn. The area under the ROC curve for ST2 ED measurements was 0.81 (95%CI 0.60-0.93). In univariate Cox

regression analysis ST2 levels at presentation significantly predicted in-hospital mortality (HR 1.11; 95%CI 1.06-1.17 for every additional 10 ng mL^{-1}, p<0.01)). This predictive potential persisted after adjustment for ADHERE risk factors and BNP values at admission (HR 1.11; 95%CI 1.05-1.17 for every additional 10 ng mL^{-1} , p<0.01).

ST2 levels and long-term survival status

Overall, 69 (33%) patients died during the observational period. Patients dying during follow up were significantly older than survivors, suffered from more severe heart failure symptoms at presentation (median NYHA class 4 vs. 3, p=0.01), were more likely to have chronic kidney disease and were less likely to be treated with beta-blockers or renin-angiotensin-aldosterone-system (RAAS) blocking agents at discharge. ST2 (median 108 [IQR: 75-185] vs. 69 [IQR: 42-99] ng mL^{-1}, p < 0.01), BNP (median: 1763 [IQR1015-3214] vs. 1333 [IQR 650-2005] pg mL^{-1}, p<0.01) and troponin T (median: 0.04 [0.02-0.07] vs. 0.01 [0.01-0.03], p<0.01) levels at presentation were significantly higher in decedents than in survivors.

To assess the potential of ED measurements of ST2 to predict mortality a receiver operating characteristics curve was drawn. The area under the ROC curve for ST2 ED measurements was 0.73 (95%CI 0.63-0.83) (Table 2); similar to the predictive potential of a clinical prediction model (model 0) based on ADHERE risk factors and BNP (AUC 0.74; 95%CI 0.65-0.85). The addition of ST2 values to this clinical risk score tended to improve the prognostic accuracy further (AUC 0.80; 95%CI 0.71-0.89) (model 1).

ST2 changes during the first 48 hours and survival status

The impact of heart failure therapy during the first 48 hours on ST2 levels was assessed. The median ST2 decrease during the first 48 hours of in-hospital treatment was 33% [-11% - -45%]. Using a categorical stratification of patients according to

tertiles of 48-hour ST2 changes clearly separated survivors from non-survivors **(Figure 1)**. Importantly, ST2 levels decreased more significantly in survivors than in non-survivors. It should be noted, that the decrease in ST2 was independent of age (r=0.65;p=0.46), systolic blood pressure (r= -0.46; p=0.66), LVEF (r=0.05; p=0.61), absolute ST2 (r=-0.1; p= 0.29), troponin T (r=0.38; p=0.82), BNP levels in the ED (r=0.01; p=0.98), the presence of atrial fibrillation (p=0.63) and the cumulative dose of beta-blockers administered during the first 48 hours (r=-0.11, p= 0.29). However, there was a weak albeit significant correlation between ST2 changes and the cumulative dose of diuretics administered during the first 48 hours (r=0.18; p=0.04) and a negative correlation with heart rate at presentation (r= -0.19; p=0.03).

In a Cox regression analysis the percentage change of ST2 over the first 48 hours significantly predicted long-term mortality in univariate analysis (HR 1.05; 95%CI 1.02-1.08 for every increase of 10%; p<0.01). In multivariable Cox regression analysis, the predictive potential of early ST2 changes persisted after the adjustment for ADHERE risk factors (blood urea nitrogen, systolic blood-pressure and serum creatinine), traditional markers of inflammation (total white cell count and high-sensitive C-reactive protein), BNP, troponin T and ST2 levels in the ED, percentage BNP changes during the first 48 hours as well as the cumulative diuretic dose administered during the first 48 hours (HR 1.07; 95%CI 1.02-1.12 for every increase of 10%; p<0.01).

In ROC curve analysis, the addition of early ST2 changes to the clinical prediction model achieved an AUC of 0.79 (95%CI 0.70-0.88) (model 2). Comparable to the AUC achieved by model 1 (AUC 0.80; 95%CI 0.71-0-89, p vs. model 1 =0.76). In IDI analysis model 2 significantly improved the risk stratification over the baseline model (model 0). Absolute integrated discrimination improvement was 0.04, relative integrated discrimination improvement was 0.25 (p=0.005).

However, the combined assessment of baseline ST2 and early ST2 changes provided further prognostic information in excess of baseline ST2 levels at presentation and the clinical model as shown in **Table 2**. Model 3 improved the area under the ROC curve to 0.84 (95% CI 0.77-0.92). Similarly, in IDI analysis, risk stratification was improved by model 3; absolute IDI for model 3 versus model 0 was 0.18, yielding a relative IDI of 1.0 ($p<0.001$) (**Figure 2)**, while for model 3 versus model 2 absolute and relative IDI were 0.13 and 0.6, respectively ($p<0.001$).

Association of early ST2 changes, treatment at discharge, and long-term mortality

At discharge 83% of patients were treated with a diuretic, 77% of patients were treated with a RAAS blocking agent and 64% of patients received a beta-blocker. In the overall patient population beta-blocker treatment ($p<0.01$) and RAAS blockade ($p<0.01$), but not diuretic therapy, was significantly associated with improved one-year survival.

To assess the association between early ST2 changes, treatment at discharge, and one-year mortality we divided patients into groups depending on their early ST2 response (responders: ST2 decrease ≥25%; non-responders: ST2 decrease < 25%) and their beta-blocker, RAAS blockade or diuretic treatment status at discharge. **Table 3** shows the baseline characteristics of ST2 responders and non-responders. **Figure 3** shows the respective Kaplan-Meier curves.

RAAS blockers at discharge were associated with survival independent of ST2 response, whereas the association of beta-blockers with survival differed markedly according to ST2 response with beneficial effects restricted to ST2 non-responders (p for interaction beta-blockers =0.04). A similar albeit non-significant trend was observed for diuretics (p for interaction diuretics =0.11).

Non-responders not receiving the beta-blocker treatment at discharge experienced an annual mortality rate of around 70%. In ST2 non-responders beta-blocker treatment was associated with a significant decrease in one-year mortality to

22%, equaling the mortality rate of ST2 responders receiving beta-blocker therapy (treated responders versus treated non-responders beta-blockers: p-log-rank=0.62). In contrast beta-blocker therapy was not associated with improved one-year mortality rates in ST2 responders (p-log-rank= 0.10). Similar trends could be observed for diuretic therapy. The association with survival for beta-blocker and diuretic therapy in ST2 non-responders was independent of LVEF and persisted in patients with preserved LVEF (beta-blockers: p-log-rank=0.79; diuretics: p-log-rank=0.73).

Discussion

In this investigation we specifically examined the potential of ED and serial measurements of ST2 to assess long-term mortality. Additionally, we investigated the association of long-term heart failure therapy with one-year mortality according to early ST2 changes in patients presenting with AHF.

We report six major findings. First, levels of ST2 at presentation to the ED are significantly associated with mortality. Second, early ST2 changes over the first 48 hours are also significantly associated with long-term mortality. Third, early ST2 changes provide additional prognostic information when assessed in combination with clinical risk stratification models. Fourth, therapy with beta-blockers at discharge might be associated with a beneficial effect on mortality in ST2 non-responders. While this association with improved survival for beta-blocker cannot be seen in ST2 responders. Fifth, the association of RAAS blocking agents with survival appears to be independent of the ST2 response.

Our results extend and corroborate previous studies assessing the association between ST2 levels measured in patients presenting with acute dyspnea to the ED and mortality. Januzzi et al. were the first to report the prognostic potential of ST2 using a first generation assay and found ST2 levels to be significantly higher in one-year decedents than survivors (21). Similar results were reported from two subsequent studies using the second generation Presage ST2 assay (15,22). Importantly, these studies consistently found ST2 measurements at presentation to independently predict all-cause mortality (15,21).

Our findings extend and corroborate the only previous study regarding early ST2 changes during AHF hospitalization (23). Boisot et al. collected ST2 samples at 6 time points throughout the in-hospital period of 150 AHF patients and found ST2 changes between admission and discharge to be predictive of 90-day all-cause mortality. Patients showing in-hospital ST2 changes of less than 15.5% experienced a

90-day mortality of 33%, while patients exhibiting ST2 decreases over 15.5% displayed a significantly lower 90-day mortality rate of 7%. Importantly Boisot et al. found ST2 levels to reach their lowest levels after 4 days of AHF therapy. Our study adds to these findings by shortening the observational period for ST2 changes to occur to 48 hours. Importantly, 48-hour risk-stratification was independent of conventional risk factors.

In contrast to the stable chronic heart failure setting, none of the drugs currently used at ED presentation, during in-hospital treatment, or at hospital discharge in patients with AHF has been shown to improve outcome (2). We therefore tried to assess the potential of biomarker signaling as a novel approach to individualize treatment at hospital discharge. Beta-blockers and RAAS blocking agents build the backbone of modern therapy in stable patients with chronic heart failure and reduced ejection fraction (2)(24-27). Their utility in AHF patients and particularly the time point to initiate these drugs is unknown. Additionally, in the face of an ever aging, highly comorbid patient population (3), in whom cardiovascular polypharmacy is associated with considerable challenges (4), a stepwise initiation and up-titration of the guideline approved chronic heart failure therapy might be necessary. Short primary in-hospital stays, prohibiting a stepwise initiation of chronic heart failure therapy, further amplify this problem (28). In the face of these challenges, clinicians are left with the difficult choice of selecting a primary drug class before subsequently adding all guideline recommended therapies. As AHF syndromes differ greatly both in phenotype as well as disease severity from each other, beta-blocker therapy at discharge may well be more beneficial in some patients than in others. Similar uncertainty underlies the use of diuretics at hospital discharge. While the widespread use of diuretics (29) relies on forced diuresis and rapid symptom relief, various studies have reported an association between diuretic use at discharge and increased patient mortality (30-32). In this non-randomized study of AHF patients RAAS blocking agents were associated with one-

year survival independent of the early ST2 response. However, we observed beta-blocker therapy to be primarily associated with survival in the ST2 non-responder subgroup. Additionally, our data hint towards a potential beneficial effect of long-term diuretic use in early ST2 non-responders. It is noteworthy that no association with survival could be observed for either beta-blocker or diuretic therapy in ST2 responders. Importantly, these findings persisted after adjusting for LVEF and might open the door to a promising new application of early ST2 changes in the long-term therapy guidance of AHF patients.

Circulating ST2 levels in AHF integrate inflammatory signals and cardiac strain: the ST2 gene (T1, IL1RL1 or Fitt1) is a member of the interleukin-1 receptor host defence family which serve as a gateway to proinflammatory signalling pathways (10). The transmembrane ST2 isoform (ST2L) has been shown to modulate T helper 2 cell activity (33) and to be involved in the development of immunologic tolerance (34). Additionally, recent studies displayed the anti-fibrotic and anti-hypertrophic effects of IL33 to be mediated by the ST2L/IL33 complex (35,36). Importantly, the cardioprotective effects of IL33 seem to be caused by a direct anti-inflammatory effect on cardiac myocytes (35).

In contrast to the cardioprotective effects of ST2L/IL33 signalling, the soluble ST2 isoform appears to act as an IL33 decoy receptor (35,37). By scavenging circulating IL33 the soluble ST2 isoform inhibits ST2L/IL33 induced cardioprotection. In addition, soluble ST2 is secreted by cardiac myocytes in response to mechanical stretch and volume overload (38). Hence, ST2 non-responders are characterized by persistent inflammation, inhibited cardioprotection and hypervolemia.

We hypothesize that the association with survival seen for beta-blocker and diuretic therapy in ST2 non-responders may directly represent the anti-inflammatory and volume-depleting effects of these drug classes. In fact, metoprolol has been shown to reduce the secretion of the proinflammatory cytokines TNFá, IL1â and IL6.

The extent of this cytokine inhibition correlates with the degree of hemodynamic improvement in human metoprolol treated heart failure (12). Similar anti-inflammatory and antioxidant effects have been described for carvedilol and bisoprolol (13,14).

Several limitations merit consideration. First, this was an observational single center study and patients who died were less likely to be prescribed RAAS blocking agents and beta-blockers, were older, and had poorer renal function. However since baseline characteristics, the prescription rates of heart failure therapies, mortality rates and the predictive potential of ED and serial ST2 measurements closely mimic those of previous studies (15,21-23,39-41) we consider our patient population to be representative. Furthermore, the association of ED and serial measurements with mortality remained statistically significant after the adjustment of baseline differences and important heart failure risk predictors. Second, we did not assess outpatient treatment during follow up, but relied on the treatment information at hospital discharge. While discharge therapy in this study was comparable to the results of the EuroHeart Failure Survey II (39) we cannot comment on the effect of possible therapy changes during follow up. Fourth, due to the design of the study and the small number of patients receiving aldosterone blocking agents at discharge at the time of patient enrollment, we cannot comment on the association between early ST2 changes and long-term aldosterone blockade. This aspect warrants further study. Fifth, treating physicians were blinded to the ST2 test results. We can therefore not assess the impact of a biomarker guided treatment strategy on heart failure drug prescription rates, treatment costs and long-term outcome. Further large scale observational and eventually randomized controlled studies will be necessary to substantiate the hypotheses derived from this study.

In conclusion, ED and serial ST2 measurements are strong and independent predictors of one-year mortality in AHF.

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Table 1 **Baseline characteristics in Survivors and Decedents with Acute Heart Failure**

	All patients (n=207)	Survivors (n=138)	Decedents (n=69)	p Value
Age in years – median (IQR)	80 (74-85)	79 (70-84)	83 (78-87)	0.03
Male gender – no. (%)	118 (57)	74 (54)	44 (64)	0.55
Risk factors – no. (%)				
Hypertension	152 (73)	99 (72)	53 (77)	0.52
Dyslipidemia	70 (34)	49 (36)	21 (30)	0.56
History – no. (%)				
Coronary artery disease	100 (48)	62 (45)	38 (55)	0.20
Heart failure	103 (50)	64 (46)	39 (57)	0.18
Diabetes mellitus	69 (33)	42 (30)	27 (39)	0.24
Chronic kidney disease	92 (44)	50 (36)	42 (61)	<0.01
Vital Status – median (IQR) / mean (SD)				
Heart rate – beats per minute	86 (75-102)	85 (75-100)	88 (72-103)	0.73
Systolic blood pressure – mmHg	137 (±26.9)	140 (±26.2)	130 (±27.4)	0.02
Diastolic blood pressure – mmHg	84 (±18.4)	85 (±18.5)	82 (±18.2)	0.20
Oxygen saturation – no. (%)	97 (95-98)	97 (95-98)	96 (93-98)	0.16
Outpatient Treatment at presentation – no.(%)				
Beta-blocker	123 (59)	85 (62)	38 (55)	0.39
Angiotensin converting enzyme-inhibitor	101 (49)	74 (54)	27 (39)	0.06
Angiotensin II Blocker	44 (21)	30 (22)	14 (20)	0.76
Diuretics	153 (74)	98 (71)	55 (80)	0.16
Aldosterone antagonist	24 (12)	14 (10)	10 (15)	0.36
Treatment at discharge – no. (%)				
Beta-blocker	133 (64)	101 (73)	32 (46)	<0.01
Angiotensin converting enzyme-inhibitor	123 (59)	93 (67)	30 (44)	<0.01
Angiotensin II Blocker	55 (27)	38 (28)	17 (25)	0.62
Diuretics	171 (83)	119 (86)	52 (75)	0.06
Aldosterone antagonist	35 (17)	22 (16)	13 (19)	0.48
Symptoms – no. (%)				
Weight gain	82 (46)	54 (39)	28 (41)	0.84
Chest pain	66 (32)	45 (33)	21 (30)	0.84
Laboratory test – mean (SD) / median (IQR)				

Hemoglobin (g/l)	125 (±21.2)	125 (±19.8)	122 (±20)	0.71
BNP (pg/ml)	1355 (794-2444)	1333 (650-2005)	1763 (1015-3214)	<0.01
ST2 (ng/mL)	78 (46-121)	65 (41-97)	120 (79-187)	<0.01
Echocardiographic findings * – mean (SD)				
Left ventricular ejection fraction	40 (±15.6)	40 (±15.7)	39 (±15.5)	0.84

IQR denontes interquartile range; SD denotes standard deviation ;
* echocardiography was performed in 161 patients.

Table 2	**Prediction of one-year mortality by area under the curve of receiver operating curve characteristic plot analysis**		
Parameter	**AUC**	**95% CI**	**p vs. model 0**
Model 0 (ADHERE clinical model/ BNP)	0.74	0.64-0.85	
ST2 baseline	0.73	0.63-0.83	0.76
Model 1 (ADHERE clinical model/ BNP/ ST2)	0.80	0.71-0-89	0.06
Model 2 (ADHERE clinical model/BNP/ST2% change)	0.79	0.70-0.88	0.10
Model 3 (ADHERE clinical model/ BNP/ ST2/ ST2% change)	0.84	0.77-0.92	0.02

Table 3 **Baseline characteristics of ST2 Responders and Non-Responders**

Parameter	ST2 Responders	ST2 Non-Responders	p-value
Age in years – median (IQR)	80 (74-84)	81 (75-86)	0.30
Male gender – (%)	58%	57%	0.69
History – (%)			
Coronary artery disease	48%	46%	0.88
Heart failure	55%	43%	0.16
Diabetes mellitus	30%	48%	0.04
Chronic kidney disease	47%	56%	0.15
Vital Status – median (IQR) / mean (SD)			
Heart rate – beats per minute	85 (75-110)	84 (71-96)	0.33
Systolic blood pressure – mmHg	135 (±23.6)	133 (±29.2)	0.46
Diastolic blood pressure – mmHg	85 (±20.4)	83 (±18.2)	0.61
Outpatient Treatment at presentation –(%)			
Beta-blocker	58%	62%	0.64
Angiotensin converting enzyme -inhibitor	52%	49%	0.71
Diuretics	76%	79%	0.73
Outpatient Treatment at discharge a –(%)			
Beta-blocker	67%	63%	0.71
Angiotensin converting enzyme -inhibitor	59%	61%	0.89
Diuretics	83%	85%	0.42
Laboratory test – mean (SD) / median (IQR)			
Creatinine (umol/l)	108 (81-137)	132 (86-188)	0.05
BNP (pg/ml)	1405 (851-2532)	1555 (792-3011)	0.64

ST2 (ng/mL)	84 (50-116)	74 (40-120)	0.44

Figure Legend:

Figure 1: Kaplan Meier curves stratified by tertiles of ST2 change during the first 48 hours

Figure 2: Graphic depiction of integrated discriminatory improvement (IDI) analysis. IDI can be calculated as the difference between the improvement in average sensitivity and changes in average of “one minus specificity”.

Figure 3: Kaplan Meier curves stratified ST2 response and treatment status at discharge; 3a: beta-blocker therapy, 3b: diuretic therapy, 3c: RAAS blockade.

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Figure 1

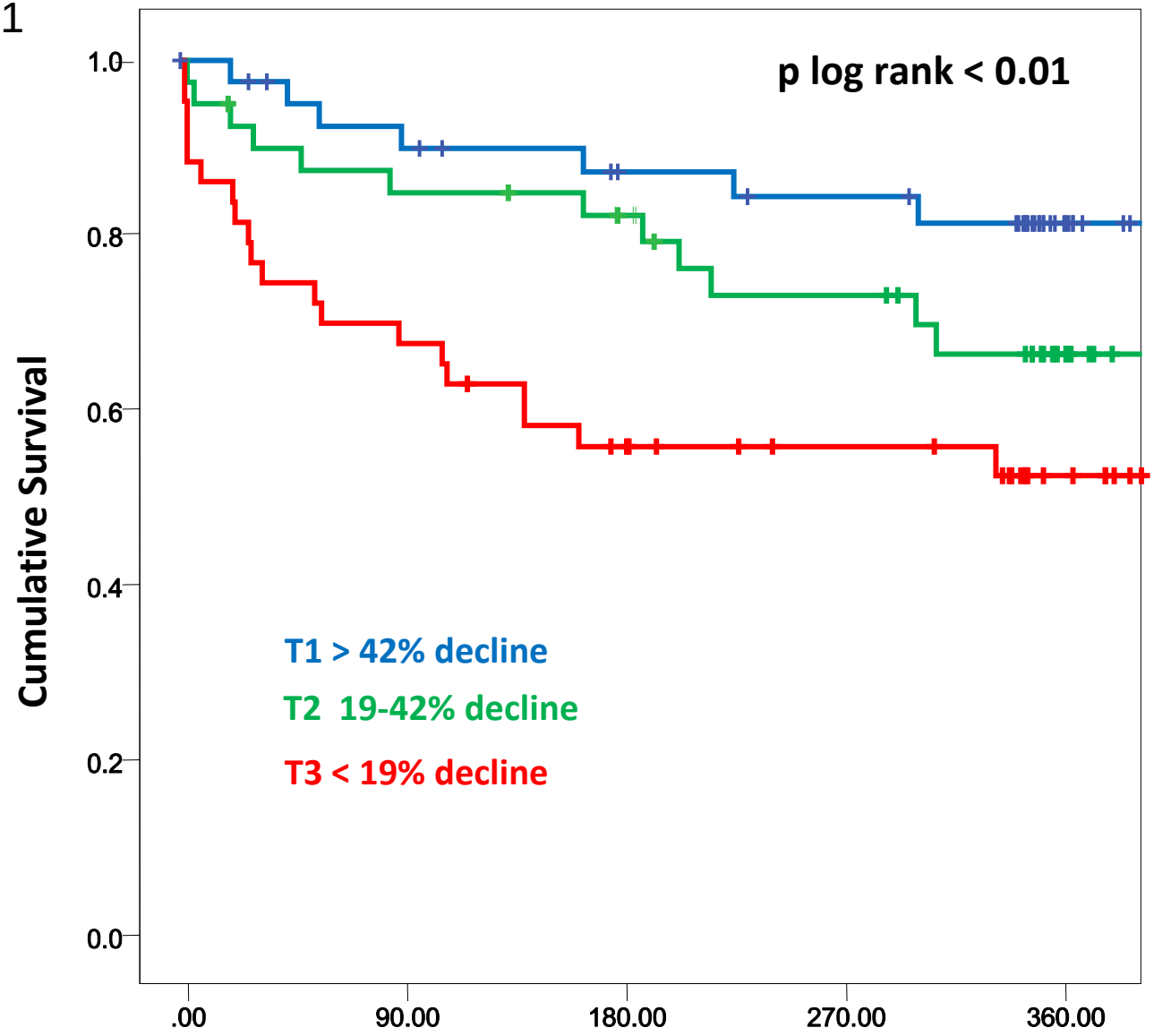

Figure 2

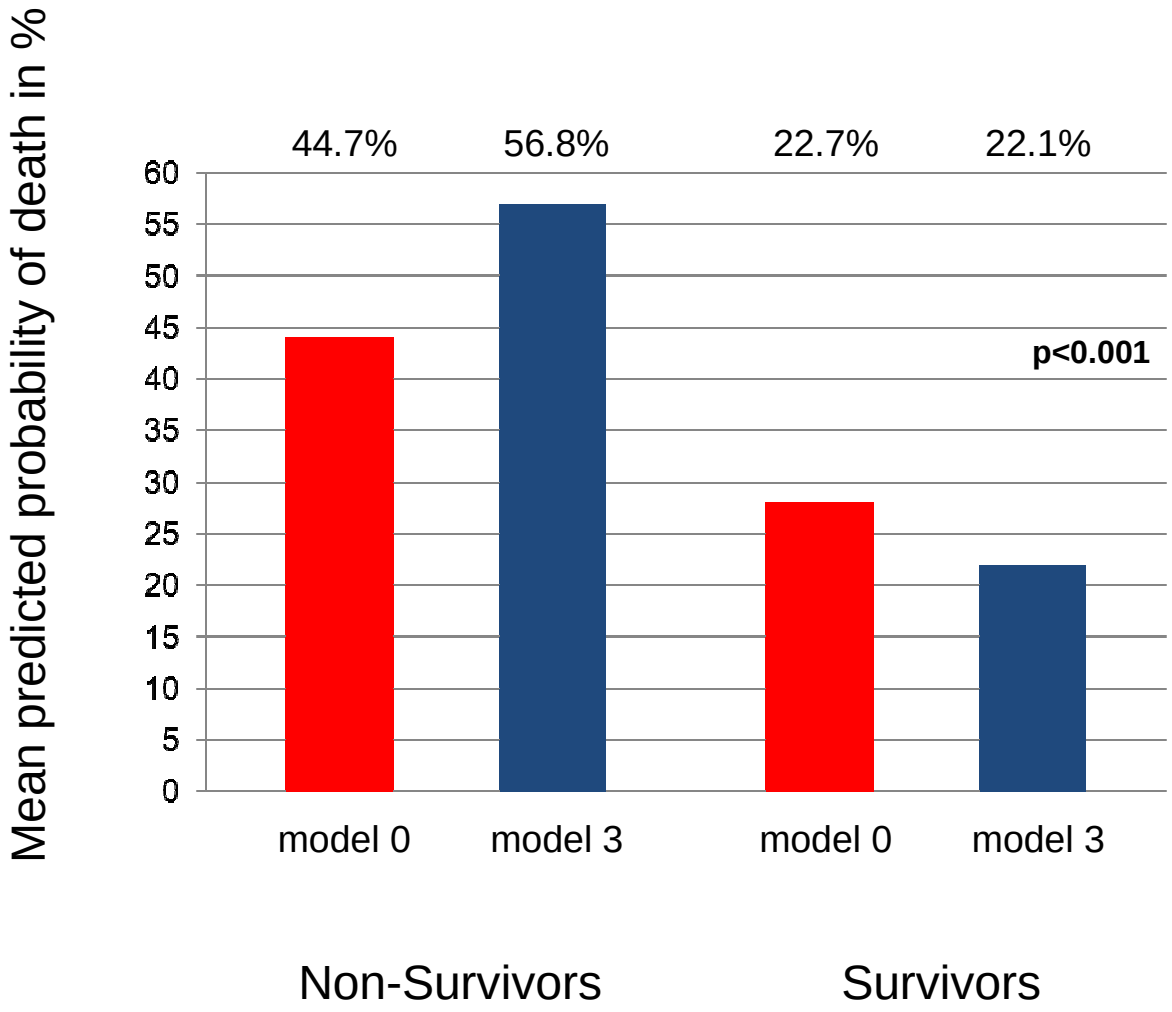
Mean predicted probability of death in %
44.7%
56.8%
22.7%
22.1%
60
55
50
45
40
35
30
25
20
15
10
5
0
p<0.001
model 0
model 3
model 0
model 3
Non-Survivors
Survivors

Figure 3a

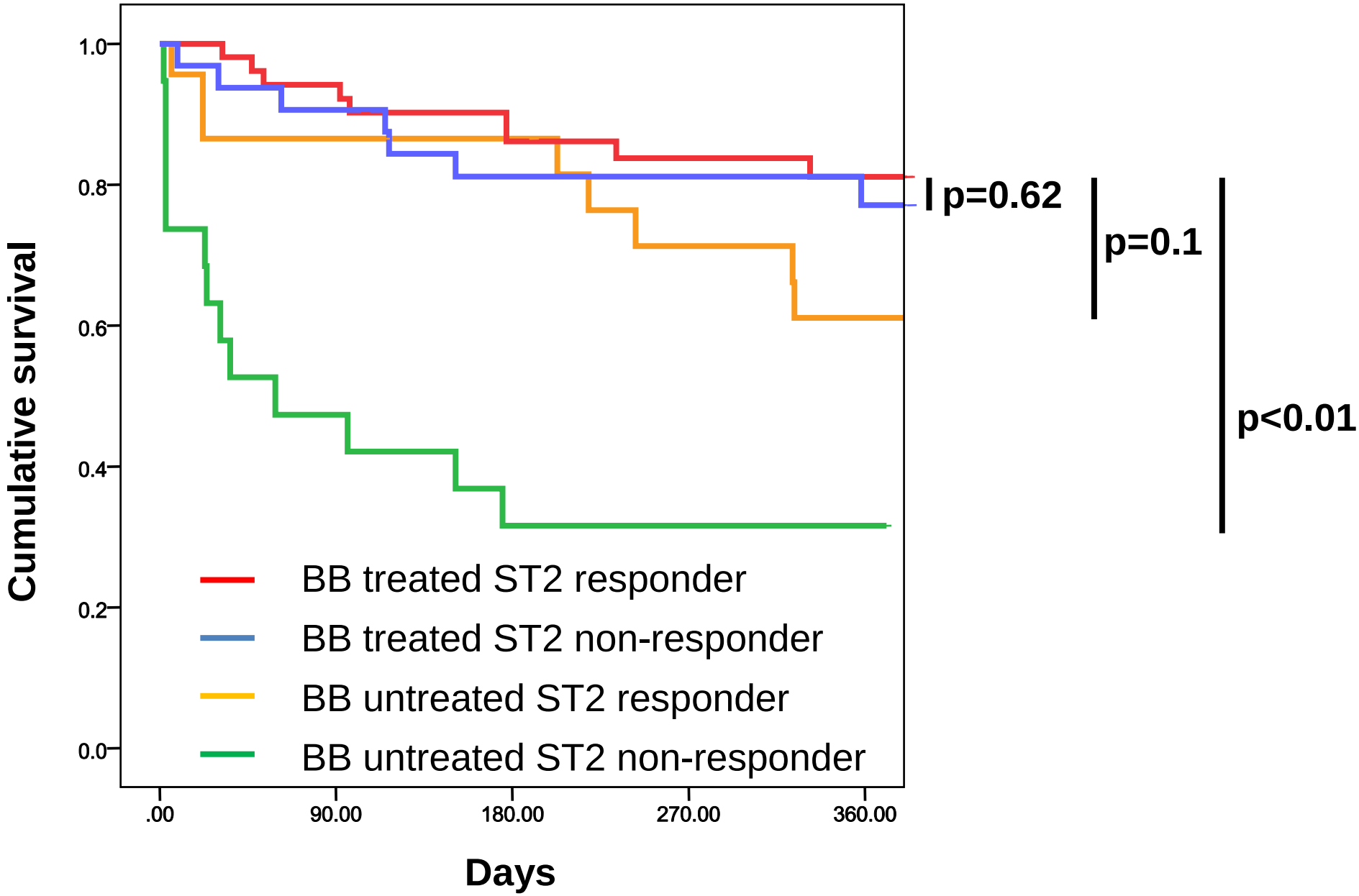

Figure 3b

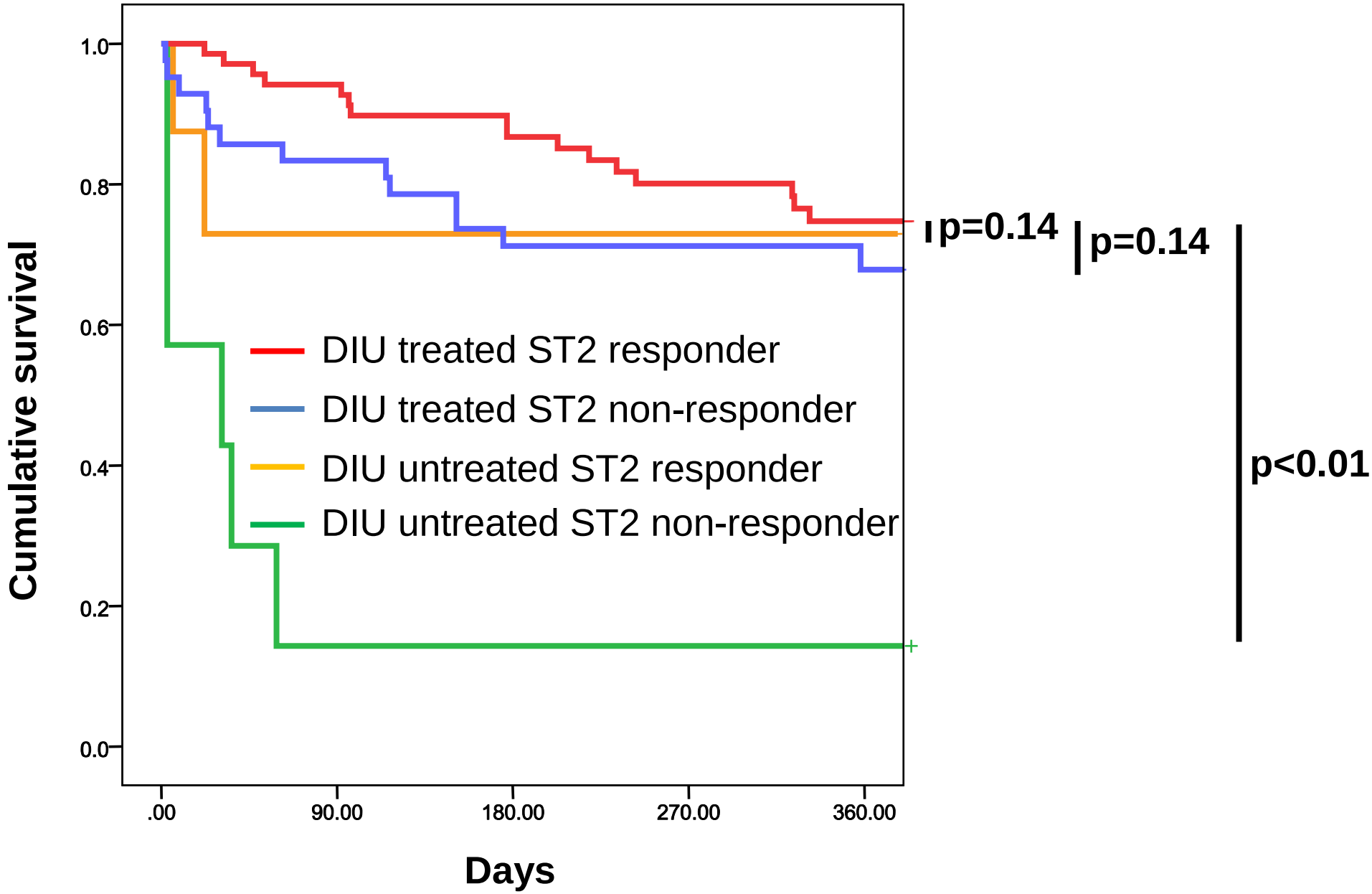

Figure 3c