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RESEARCH ARTICLE



NTproBNP and ST2 as predictors for all-cause and cardiovascular mortality in elderly patients with symptoms suggestive for heart failure

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ABSTRACT

Background: A new biomarker, suppression of tumorigenicity 2 (ST2) has been introduced as a marker for fibrosis and hypertrophy. Its clinical value in comparison with N-terminal pro-hormone of brain natriuretic peptide /Amino-terminal pro-B-type natriuretic peptide (NTproBNP) in predicting mortality in elderly patients with symptoms of heart failure (HF) is still unclear.

Aim: To evaluate the prognostic value for all-cause- and cardiovascular mortality of ST2 or NTproBNP and the combination of these biomarkers.

Patients and methods: One hundred seventy patients with clinical symptoms of HF (77 (45%) were with verified HF) were recruited from one selected primary health care center (PHC) in Sweden and echocardiography was performed in all patients. Blood samples were obtained from 159 patients and stored frozen at -70°C . NTproBNP was analyzed at a central core laboratory using a clinically available immunoassay. ST2 was analyzed with Critical Diagnostics Presage ST2 ELISA immunoassay.

Results: We studied 159 patients (mean age 77 ± 8.3 years, 70% women). During ten years of follow up 78 patients had died, out of which 50 deaths were for cardiovascular reasons. Continuous NTproBNP and ST2 were both significantly associated with all-cause mortality (1.0001; 1.00001–1.0002, $p = 0.04$ and 1.03; 1.003–1.06, $p = 0.03$), NTproBNP but not ST2 remained significant for cardiovascular mortality after adjustments (1.0001; 1.00001–1.0002, $p = 0.03$ and 1.01; 0.77–1.06, $p = 0.53$), respectively. NTproBNP above median (>328 ng/L) compared to below median was significantly associated with all-cause mortality (HR: 4.0; CI: 2.46–6.61; $p < 0.001$) and cardiovascular mortality (HR: 6.1; CI: 3.11–11.95; $p < 0.001$). Corresponding analysis for ST2 above median (25.6 ng/L) was not significantly associated neither with all-cause mortality (HR: 1.4; CI: 0.89–2.77) nor cardiovascular mortality (HR: 1.3; CI: 0.73–2.23) and no significant interaction of NTproBNP and ST2 (OR: 1.1; CI: 0.42–3.12) was found.

Conclusion: In elderly patients with symptoms of heart failure ST2 was not superior to NTproBNP to predict all cause or cardiovascular mortality. Furthermore, it is unclear if the combination of ST2 and NTproBNP will improve long-term prognostication beyond what is achieved by NTproBNP alone.

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NTproBNP; ST2; elderly; heart failure; morbidity; mortality




Introduction

Chronic heart failure (HF) occurs in 10–20% of the population aged 70–80 y (Ponikowski *et al.* 2016). The prognosis is poor for patients with HF, the need for hospitalization and cost is high (Ryden-Bergsten and Andersson 1999) and mortality is comparable with some cancer illnesses (Stewart *et al.* 2001). Elderly patients (>75 y) with symptoms of heart failure are commonly seen in primary health care (PHC) where cardiovascular disorders, such as ischemic heart disease, hypertension and heart failure are highly prevalent. Besides that, elderly patients often have serious co-morbidities and the contributions of these disorders to hospitalizations of patients with HF are common and often overlooked (Olofsson *et al.* 2007).

The need for markers or other instruments to identify patients with high risk for hospitalization or mortality is therefore urgently needed. N-terminal pro-hormone of brain natriuretic peptide (NTproBNP) or BNP are not only markers

for excluding the diagnosis (Olofsson and Boman 2010) of HF but also serve as prognostic tools for morbidity and mortality in patients with HF (Doust *et al.* 2005). However, natriuretic peptides have some drawbacks and imperfections such as high biological variation with age, renal impairment and obesity (Maisel *et al.* 2004).

A new biomarker, suppression of tumorigenicity 2 (ST2) has been introduced as a marker for fibrosis and hypertrophy and may thus be used to predict hospitalization (de Boer *et al.* 2015, Meijers *et al.* 2016). ST2 has earlier been shown to predict hospitalization for patients diagnosed with heart failure and chronic obstructive pulmonary disease (Meijers *et al.* 2016). ST2 has also been shown to be a powerful prognostic marker in patients with preserved ejection fraction (HFpEF) in patients (≈ 65 years) (Wang *et al.* 2013). The pathophysiology of HF in the elderly patients differs somewhat from that of HF in younger patients due to changes in the structure and function of the heart that are associated

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with ageing (Chen and Frangogiannis 2010). HFpEF is equally common as HF with reduced EF (HFrEF) as an underlying pathophysiological disturbance (Wang *et al.* 2013). The clinical picture of HF in the elderly, especially in women, is often associated with the condition of HFpEF (Chen and Frangogiannis 2010, Manzano *et al.* 2011). Besides that, serum ST2 level, as a nonspecific marker has also been shown to be associated with non-cardiac co-morbidities (Ather *et al.* 2012). The two biomarkers evaluated in this study, ST2 and NT-proBNP, are measures of separate and distinct biological processes which may provide independent and complementary prognostic information.

For elderly patients with symptoms of HF treated in PHCs there is a lack of knowledge about the predictive value of ST2 in comparison with NTproBNP. From this perspective our hypothesis was that ST2 or its combination with NTproBNP might be a better predictor of all-cause or cardiovascular mortality than NTproBNP alone.

Clinical significance

- Even if ST2 was significantly associated with all-cause and cardiovascular mortality it did not alone add prognostic value with the cutoff values used in our analysis beyond what was achieved with NTproBNP.
- The combination of NTproBNP and ST2 was slightly better than NTproBNP alone but its clinical value is unclear and has to be further evaluated.
- Furthermore, type of heart failure, systolic versus diastolic did not seem to have an impact on the usefulness of ST2 in the clinical setting.

- FDA has recommended 35 ng/mL as a clinical cutoff for estimating risk and often used in clinical practice.
- In present study a cutoff level of 32 ng/mL was used and the results for all-cause- and cardiovascular mortality were quite similar.

Aim

Our primary aim for this study was to evaluate the prognostic value of each biomarker ST2 and NTproBNP; and secondly the combination of these biomarkers in elderly patients with symptoms of heart failure.

Methods

Study population

The study population and diagnostic procedures of the patients with HF has been described in detail previously (Olofsson *et al.* 2007). In short, between the years 2000 and 2003, 170 patients with clinical symptoms of HF were recruited from one selected PHC with a catchment area of 7800 in the northern Sweden (Figure 1). For administrative reasons, blood samples for NTproBNP and ST2 could be obtained only in 159 patients, which constituted the present study cohort. The PHC had a computer-based registry for patients with a diagnosis of clinical symptoms of HF. This study comprises patients from the registry as well as consecutive patients who were identified by the general practitioner (GP). All patients had symptoms, essentially breathlessness, that in the GP's clinical judgment could be caused by chronic HF (Olofsson *et al.* 2007).

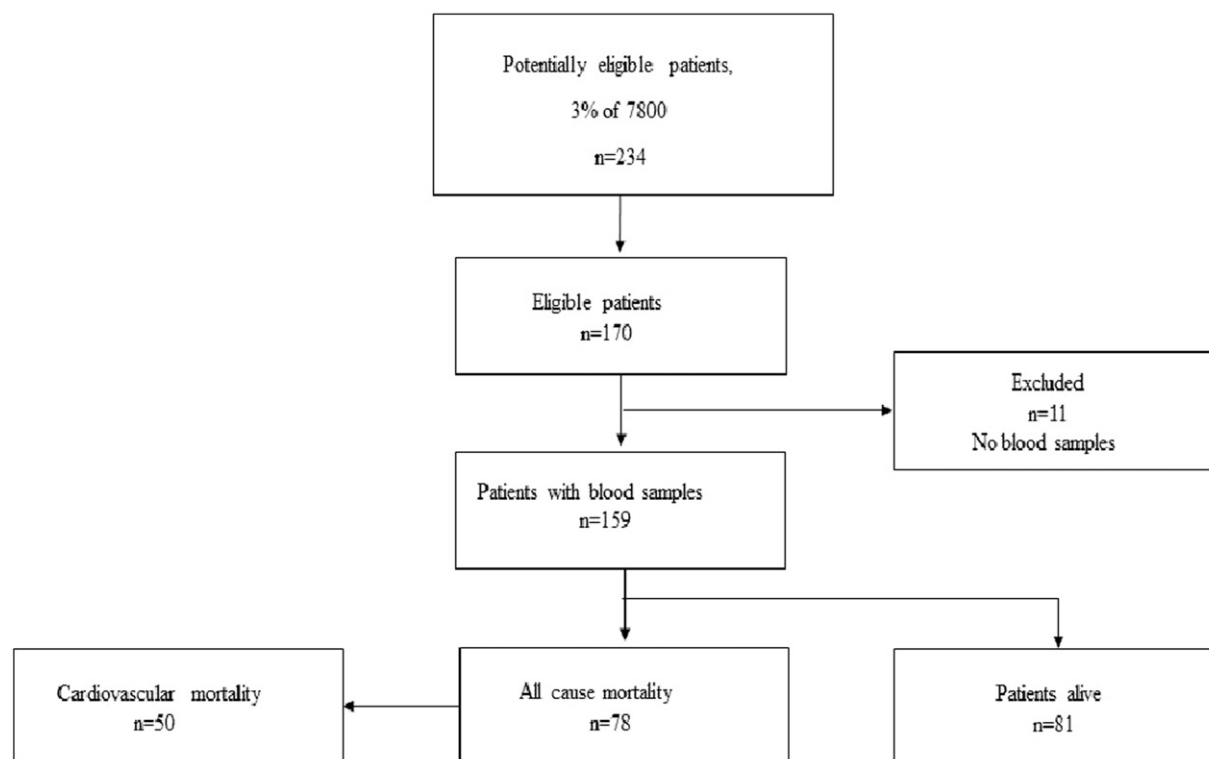


Figure 1. Flowchart of 234 potentially eligible and 170 eligible patients, of whom 159 had blood samples for analysis. All 159 patients had a 10-year follow-up (median: 7.6 years).

The GP registered data from the examination of the patient into a pre-specified HF record. Patients then were referred for an echocardiography (performed by MO) and subsequent cardiovascular consultation. The study cardiologist (KB) confirmed or refuted the diagnosis of HF according to European Society of Cardiology guidelines (Remme and Swedberg 2001) based on the GP's pre-specified HF record, echocardiography results and hospital records. Clinical evaluation of these patients revealed that confirmed HF was verified in only 45% of the patients and was significantly more common in men than women. 16% of patients had a verified systolic or diastolic HF, respectively and 12% had a combined systolic and diastolic HF (Olofsson *et al.* 2007). The reference group (39%) consisted of patients with no heart failure. With careful clinical evaluation with echocardiography we found a group of 25 patients with only systolic or diastolic dysfunction but without clinically relevant symptoms, hence they did not fulfill the criteria for a diagnosis of true heart failure (Olofsson *et al.* 2007). Underlying heart disease included patients with myocardial infarction, hypertension, atrial fibrillation (AF), ischemic heart disease, angina pectoris and those with a cardiac murmur as a proxy for valvular disease (eight patients with mitral insufficiency, four with aortic stenosis and three with aortic insufficiency; 11 patients had non-specified cardiac murmurs). AF was verified by an electrocardiogram analysis. The diagnosis of HF was validated with echocardiography. Overall HF was defined as all patients with systolic and/or diastolic heart failure. No other clinical variables were validated. There were missing values for smoker, ex-smoker ($n = 10$) and alcohol ($n = 16$). All other categorical variables were classified as yes or no.

Biomarkers

Blood sampling took place before the echocardiographic examination from fasting patients who had rested for 20 min. After 5 min, the samples were centrifuged for 10 min at 4 °C and were later stored frozen at −70 °C. Amino-terminal pro-B-type natriuretic peptide (NT-proBNP) was analyzed at a central core laboratory using a clinically available immunoassay (Roche Elecys, Roche Diagnostics, Basel, Switzerland) (Roche Diagnostic Corporations 2002). ST2 was analyzed with Critical Diagnostics Presage ST2 ELISA immunoassay (Presage ST2 Assay, Critical Diagnostics, San Diego, CA), with a lower limit of detection of 2 ng/mL, an upper limit of detection of 200 ng/mL, an intra-assay coefficient of variation <2.5% and an inter-assay coefficient of variation of <4.6%. The core laboratories were blinded to all clinical data.

Outcome classification

Death certificates were used to identify all-cause mortality and cardiovascular mortality and defined as International Classification of Diseases-10 codes I00–I99 for the 10-year follow-up (median: 7.6 years) for the 159 patients in this study.

Statistics

Baseline characteristics were described as frequencies or mean and standard deviation or median and quartiles. Differences between groups were tested with Student's t-test for normally distributed data, Mann Whitney for non-normally distributed continuous variables and with Chi square for categorical variables. Pearson's correlation coefficient or Spearman's rho were appropriate, used to analyze correlations. For association between baseline characteristics and mortality, we used Cox regression analysis. Adjustments were made from fixed factors as age, gender and smoking habits, which we found in an earlier analysis of the present cohort. (Olofsson and Boman 2015). In addition we included only significant variables namely kidney dysfunction and all HF from the univariable Cox regression analysis. All other baseline characteristics did not reach statistical significance. Continuous variables of ST2 and NTproBNP were used. For clinical decisions of NTproBNP and ST2, medians and quartiles were explored. Assumption of proportional hazard was verified graphically using Kaplan-Meier survival curves for ten years mortality. For test of interaction of NTproBNP and ST2 above and below median values were used in the SPSS software test of interaction, marked as '>a*b>'. A p value <0.05 was regarded as statistically significant. PASW statistics version 18.0 (SPSS, Chicago, IL) was used for all statistical analyses.

Patients signed written consent and the study was approved by the Committee of Ethics at Umeå University (diary number 00-276).

Results

We studied 159 patients, mean age 77 years, out of which 111 (70%) were women. During 10 years of follow up 78 (49%) patients had died, of which 50 deaths were (64%) for cardiovascular reasons. Baseline characteristics of those who survived and those who died are presented in Table 1. Patients who died were older, had more often kidney dysfunction, heart failure, systolic but not diastolic HF. Mean levels of NTproBNP and ST2 were significantly higher among those who died, see Table 1.

There was a significant correlation between NTproBNP and ST2 ($r = 0.22$; $p = 0.007$). NTproBNP also correlated significantly with kidney dysfunction ($r = 0.26$; $p = 0.001$); overall HF ($r = 0.28$; $p = 0.001$) and age ($r = 0.25$; $p = 0.003$), while ST2 was not significantly correlated with any of these variables although borderline for all HF ($r = 0.16$; $p = 0.06$).

Uni- and multivariable Cox regression analysis

Results of uni- and multivariable Cox regression analysis for all-cause and cardiovascular mortality are presented in Table 2. Continuous NTproBNP and ST2 were both significantly associated with all-cause mortality but only NTproBNP remained significant for cardiovascular mortality after adjustments.

Table 1. Baseline characteristics of those who were alive ($n = 79$) and those who had died ($n = 80$) after 10 years of follow-up.

	<i>n</i>	Alive Mean (SD) or <i>n</i> (%)	Dead Mean (SD) or <i>n</i> (%)	<i>p</i> value
Age (years)	159	74 ± 8.5	81 ± 6.8	<0.001
Female	111	58 (52)	53 (47)	0.389
Weight (kg)	152	75 ± 16.5	72 ± 14.6	0.243
Smoker or ex-smoker	37	15 (41)	22 (59)	0.256
History of alcohol	31	18 (58)	13 (42)	0.399
History of diabetes	20	7 (35)	13 (65)	0.231
History of hypertension	63	32 (51)	31 (49)	0.872
History of myocardial infarction	30	13 (43)	17 (57)	0.544
History of atrial fibrillation	21	7 (33)	14 (67)	0.234
History of valvular disease	25	11 (44)	14 (56)	0.664
History of underlying heart disease	129	61 (47)	68 (53)	0.230
History of stroke	18	7 (39)	11 (61)	0.454
History of pulmonary disease	19	9 (47)	10 (53)	1.000
Kidney dysfunction, (Creatinine >100 µmol/L)	35	25 (71)	10 (29)	0.006
Overall HF	72	29 (49)	43 (60)	0.015
Reference group	61	38 (62)	23 (38)	0.015
NTproBNP, median, Q1–Q3, ng/L	159	190, 108–349	599, 269–1428	<0.001
ST2, median, Q1–Q3 (ng/L)	157	25, 20–29	27, 23–34	0.231
ACE or ARB and BB	135	69 (51)	66 (49)	0.507

Table 2. Univariable and multivariable analysis of NTproBNP and ST2 for all-cause and cardiovascular mortality.

Variable	All-cause mortality				CVD mortality			
	Univar. (HR; CI)	<i>p</i> value	Multivar. (HR; CI)	<i>p</i> value	Univar. (HR; CI)	<i>p</i> value	Multivar. (HR; CI)	<i>p</i> value
Age, year	1.1; 1.05–1.12	0.000	1.12; 1.06–1.18	0.000	1.2; 1.11–1.24	0.000	1.22; 1.13–1.32	0.001
Gender	1.3; 0.79–2.09	0.33	–	–	1.2; 0.65–2.17	0.58	–	–
Smoking	1.6; 0.96–2.60	0.07	4.27; 2.22–8.23	0.000	1.5; 0.79–2.83	0.22	6.01; 2.54–14.2	0.000
Kidney dysf.	2.3; 1.43–3.74	0.01	2.12; 1.08–4.17	0.03	2.9; 1.62–5.25	0.000	2.33; 1.03–5.27	0.04
Overall HF	2.0; 1.20–3.31	0.01	–	–	2.2; 1.22–4.38	0.01	–	–
NTproBNP (ng/L)	1.0001; 1.0001–1.0002	0.000	1.0001; 1.00001–1.0002	0.04	1.0001; 1.0001–1.0002	0.000	1.0001; 1.00001–1.0002	0.03
ST2 (ng/L)	1.03; 1.01–1.05	0.000	1.03; 1.003–1.06	0.03	1.03; 1.002–1.05	0.04	1.01; 0.77–1.06	0.53

CVD: cardiovascular disease; univar.: univariable; multivar.: multivariable; HR: hazard ratio; CI: confidence interval; HF: heart failure; Kidney dysf.: kidney dysfunction = creatinine >100 µmol/L; NTproBNP: N-terminal pro-hormone of brain natriuretic peptide; ST2: suppression of tumorigenicity 2.

Medians and quartiles

NTproBNP above median (>328 ng/L) compared to below median was significantly associated with all-cause mortality (HR: 4.0; CI: 2.5–6.6; $p < 0.001$) and cardiovascular mortality (HR: 6.1; CI: 3.1–12.0, $p < 0.001$). Corresponding analysis for ST2 above median (25.6 ng/L) was not significantly associated neither with all-cause mortality (HR: 1.4; CI: 0.9–2.8) nor cardiovascular mortality (HR: 1.3; CI: 0.7–2.2).

Association of quartiles of NTproBNP with all-cause mortality showed increasing HRs over quartiles; Q2 vs. Q1 (HR: 3.1; CI: 1.2–7.9; $p = 0.19$); Q3 vs. Q1 (HR: 5.5; CI: 2.3–13.5; $p < 0.001$) and Q4 vs. Q1 (HR: 11.7; CI: 4.9–28.2; $p < 0.001$) (Figure 2). For cardiovascular mortality NTproBNP, Q4 (≥ 893 ng/L) vs. Q1 was significantly associated (HR: 16.2; CI: 5.6–46.8, $p < 0.001$). Corresponding HRs for quartiles of ST2 for all-cause mortality; HR for Q2 vs. Q1 was higher than for Q3 vs. Q1; (HR: 2.1; CI: 1.0–4.1; $p = 0.39$) and (HR: 1.1; CI: 0.5–2.3; $p = 0.886$), respectively (Figure 3). The association of Q4 (≥ 32 ng/L) vs. Q1 was significant (HR: 3.6; CI: 1.9–7.0; $p < 0.001$) as was ST2 Q4 vs. Q1 for cardiovascular mortality (HR: 3.8; CI: 1.7–8.6; $p = 0.001$).

ROC-analysis

The area under curve for all-cause mortality was for NTproBNP (0.79; CI: 0.72–0.86; $p < 0.001$) and for ST2

(0.63; CI: 0.54–0.71; $p = 0.007$). For NTproBNP a value of 252 ng/L had the best cutoff value for sensitivity and specificity of 82 and 65%, respectively. Corresponding value for ST2 was 19.8 ng/L with a sensitivity and specificity of 91 and 24%, respectively.

Interaction analysis and cutoff values

An interaction analysis of associations of four groups above and below median and for all-cause and cardiovascular mortality; Group1 (reference group) = NTproBNP and ST2 below median, Group 2 = NTproBNP below and ST2 above median, Group 3 = NTproBNP above and ST2 below median and Group 4 = NTproBNP above and ST2 above median, is shown as survival plots for all-cause mortality in Figure 4. Compared with the reference group significant associations were found only for groups 3 (HR: 3.8; CI: 1.8–8.0; $p < 0.001$) and 4 (HR: 5.4; CI: 2.6–11.0; $p < 0.001$), respectively for all-cause mortality and (HR: 6.3; CI: 2.3–17.9; $p < 0.001$) and (HR: 8.3; CI: 3.1–22.2; $p < 0.001$) for cardiovascular mortality, respectively. There was no significant difference between groups 3 and 4, neither for all-cause mortality (HR: 1.4; CI: 0.8–2.4; $p = 0.21$) nor cardiovascular mortality (HR: 1.3; CI: 0.7–2.4; $p = 0.41$) and no significant interaction of NTproBNP and ST2 (OR: 1.1; CI: 0.4–3.1) was found. The US Food and Drug Administration-approved cut-off value of ST2 (>35 ng/mL) was associated with all-cause mortality (HR: 2.6; CI: 1.5–4.4) and cardiovascular mortality (HR: 0.97; CI: 0.1–7.9).

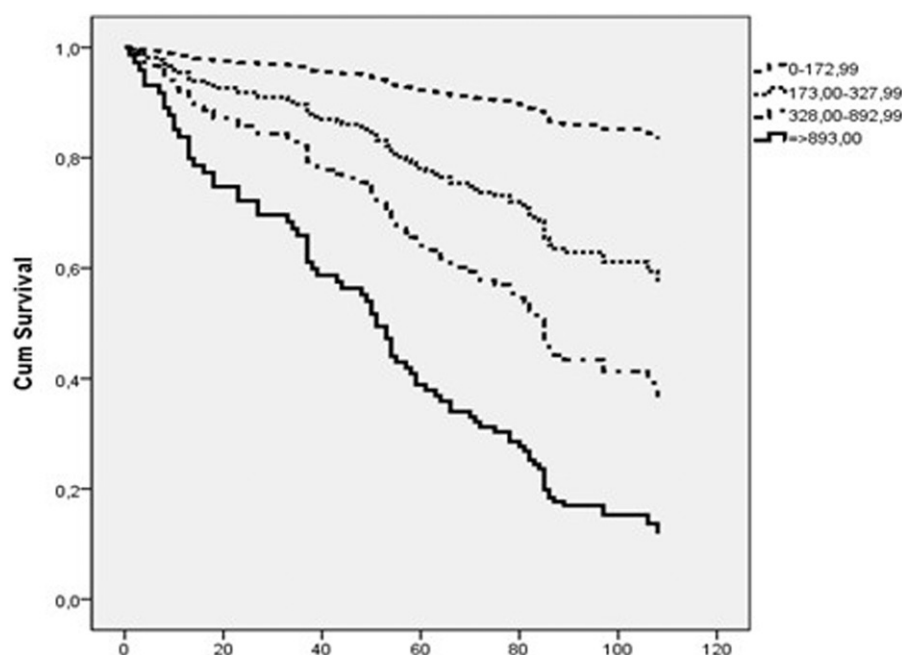


Figure 2. Survival plots of quartiles of NTproBNP on all-cause mortality after 10 years of follow-up. Reference value = quartile 1 of NTproBNP (<173 ng/L).

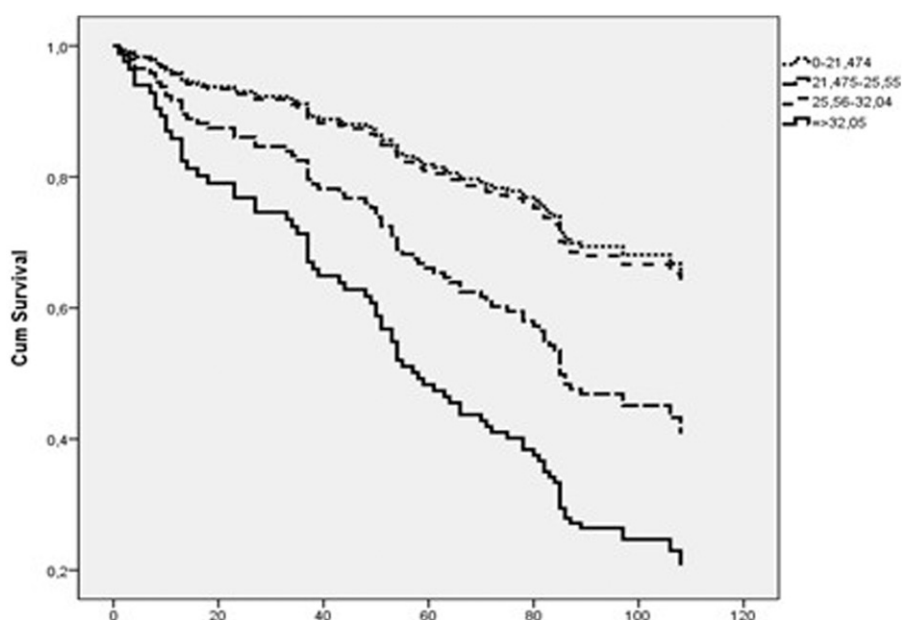


Figure 3. Survival plots of quartiles of ST2 on all-cause mortality after 10 year of follow-up. Reference value = quartile 1 of ST2 (<21.475 ng/mL).

Corresponding HRs for a cutoff value of (>32 ng/L) used in the present study were (HR: 2.8; CI: 1.8–4.5) and (HR: 1.2; CI: 0.2–6.0), respectively.

Discussion

The main finding was that ST2 was not superior to NTproBNP neither for all-cause nor cardiovascular mortality. Our hypothesis that ST2 might be superior to NTproBNP was not fulfilled. In fact, the interaction analysis of NTproBNP and

ST2 did not add any significant prognostic value to that of NTproBNP alone neither for all-cause nor cardiovascular mortality. Even if ST2 was significantly associated with mortality, explanations why ST2 did not add prognostic value above NTproBNP in our patients are unclear. We found no gradual increase of risk like among levels of NTproBNP over quartiles. A study by Daniels *et al.* (2010) found that outpatients referred for echocardiography with a high ST2 level had a significantly higher risk of death and those with elevated levels of both ST2 and B-type natriuretic peptide were at even higher risk. A difference from our study was that elevated

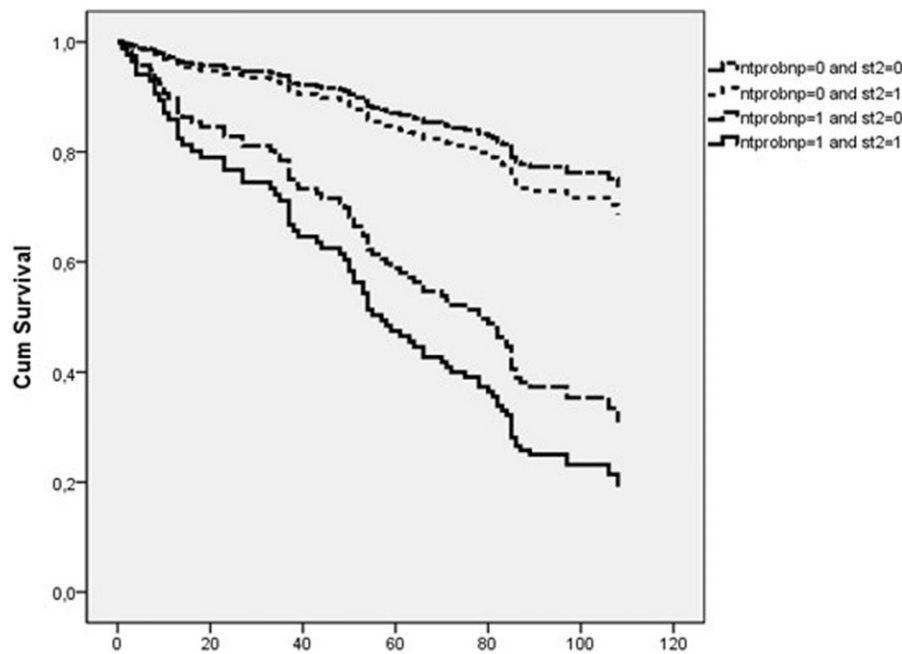


Figure 4. Survival plots of NTproBNP and ST2 below or above medians for all-cause mortality after 10 years of follow-up. Reference value = NTproBNP (<328 ng/L) and ST2 (<25.56 ng/mL) below medians is = 0. Values for NTproBNP and ST2 equal or above median are denoted as = 1.

ST2 levels in their study mainly reflected right-side heart size and function. In our original study only 45% had a verified heart failure (systolic and/or diastolic) and 16% had either a systolic or diastolic HF while signs of right-side failure were not investigated (Olofsson *et al.* 2007).

Our results differed from the study of Pascual-Figal *et al.* (2009), who found that elevated ST2 concentrations provided additional prognostic value to NTproBNP levels and they suggested that a combined biomarker approach may be of help in decision making (Pascual-Figal *et al.* 2009). There are a number of important differences between their study and ours as their patients were much younger, had systolic heart failure ($EF \leq 45\%$) and their main outcome was sudden cardiac death. One important difference was that less than half of our patients had a verified heart failure, systolic and/or diastolic. Our reference population was, however, not free from cardiovascular disorders. Many had hypertension, ischemic heart disease or atrial fibrillation which may have had an impact on the distribution of ST2 levels. The question is also the importance and difference between ST2 and natriuretic peptides on the pathophysiological mechanisms of HF in the elderly. Both markers are released in response to myocyte stretch (Maisel *et al.* 2004, Sanada *et al.* 2007). ST2 also functions as a decoy receptor, neutralizing its ligand interleukin (IL)-33. A central role of IL-33 in the cardiomyocyte is to protect against progressive fibrosis and hypertrophy (Sanada *et al.* 2007, Parikh *et al.* 2016). The question is whether these effects on fibrosis and hypertrophy have any additional impact on prognosis beyond what can be achieved from the reduction of natriuretic peptides. One large study on community-dwelling subjects without prevalent HF from the Cardiovascular Health Study reported only a modest predictive value of ST2 on the elderly population (Parikh *et al.* 2016). Moreover, in the adjusted analysis ST2 was not associated with any cardiac subtypes of HFpEF or HFrEF. Their

results are in accordance with our findings, although their patients were somewhat younger and without symptoms of HF. Two recent studies have added further important aspects on the prognostic role of ST2 in heart failure (Gül *et al.* 2017, Aimo *et al.* 2017). Gül *et al.* (2017) found that ST2 could be helpful for risk stratification in outpatients with HF. Their results are somewhat in contrast to our findings. Their patients were also diagnosed with HF. They were much younger, had a shorter time of follow-up and there was no results on all-cause mortality and no comparison with NTproBNP. In a meta-analysis, Aimo *et al.* (2017) reported that ST2 was of prognostic value in patients with acute heart failure primarily regarding all-cause and cardiovascular deaths. Acute heart failure differs in many respects from chronic heart failure, especially in elderly patients, the results from this meta-analysis are hardly comparable to our findings.

Limitations

There are a number of limitations of the present study. This was a *post-hoc* non-prespecified study and our results can only be regarded as hypothesis generating. There is no general agreement of the best cutoff level for either ST2 or NTproBNP but for comparison with NTproBNP we choose to use median and quartiles. Strength of our study is the long-term follow up and that all patients had echocardiographic evaluation of heart function. We chose systolic and diastolic heart failure rather than HFrEF and HFpEF but have made comparisons to studies referring to HFrEF and HFpEF. Our definitions (Benjamin *et al.* 1992) may thus differ somewhat from definitions HFrEF and HFpEF. The small number of patients and outcome, especially when comparing different groups over and below medians, may be hampered by a statistical type 2 error of the analysis. Some data for clinical variables were missing for unknown reasons. For underlying

heart diseases, missing data were regarded as absence of disease. Interpreting data of these diseases should be made with caution.

Conclusion

In elderly patients with symptoms of heart failure ST2 was not superior to NTproBNP to predict all cause or cardiovascular mortality. A combination of ST2 and NTproBNP was associated with higher, but not significant, hazard ratios for both all- cause and cardiovascular mortality. It is thus unclear if the combination of ST2 and NTproBNP will improve long-term prognostication beyond what is achieved by NTproBNP alone.

Disclosure statement

The authors report no declarations of interest.

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