



ORIGINAL ARTICLE

Soluble suppression of tumorigenesis-2 is a strong predictor of all-cause, cardiovascular and infection-related mortality risk in haemodialysis patients with diabetes mellitus

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ABSTRACT

Background. Soluble suppression of tumorigenesis-2 (sST2) is a strong prognostic biomarker of cardiovascular (CV) disease. End-stage kidney disease (ESKD) patients are at high risk of CV events and infections. Herein we investigated the utility of sST2 to predict all-cause and cause-specific mortality in haemodialysis (HD) patients with diabetes mellitus.

Methods. sST2 concentrations were measured in plasma samples of 1196 participants of the German Diabetes and Dialysis (4D) study who had type 2 diabetes mellitus and received maintenance HD for ESKD. Hazard ratios (HRs) for prespecified, adjudicated endpoints were determined according to sST2 levels at baseline by multivariate Cox proportional hazards analysis.

Results. Participants (mean age 66 years, 54% male) had a median sST2 concentration of 25 ng/mL and were followed up for 4 years. After adjustment for possible confounders, participants with sST2 concentrations in the highest (>32.6 ng/mL) compared with the lowest (<20.1 ng/mL) quartile exhibited a 2-fold higher all-cause mortality risk {[HR 2.06 95% confidence interval (CI) 1.61–2.61]; $P < .001$ }. High sST concentrations (fourth versus first quartile) were strongly associated with the risk of cardiac death [HR 2.29 (95% CI 1.55–3.39); $P < .001$]. Analysis of individual components of cardiac causes of death showed an increased risk of sudden death [HR 2.24 (95% CI 1.33–3.77); $P < .001$], death due to myocardial infarction [HR 2.12 (95% CI 0.9–5.0); $P = .087$] and heart failure [HR 3.34 (95% CI 1.15–9.75); $P = .027$] in

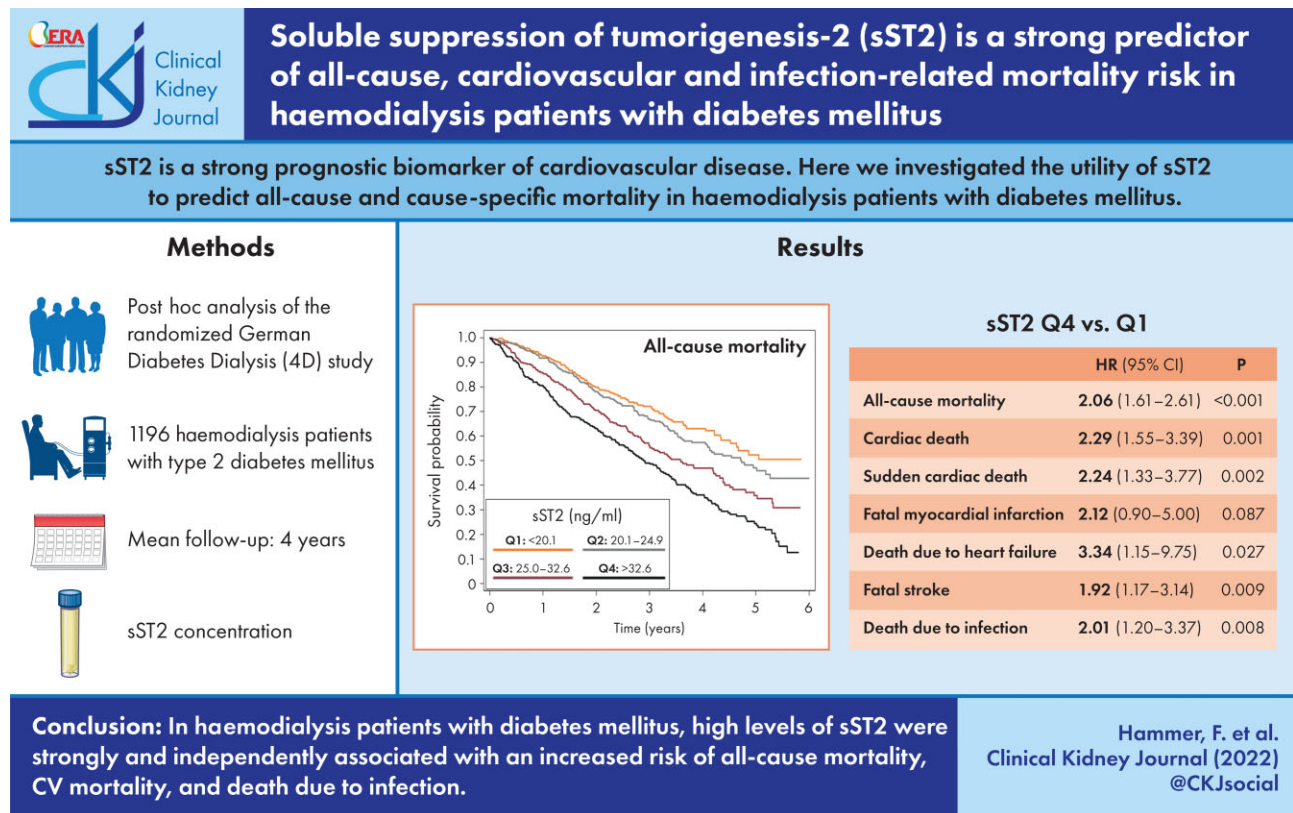
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participants with sST2 levels in the highest compared with the lowest quartile. Likewise, participants with the highest sST2 levels had an increased risk of fatal stroke [HR 1.92 (95% CI 1.17–3.14); $P = .009$] and fatal infections [HR 2.01 (95% CI 1.2–3.37); $P = .008$]. In contrast to fatal CV events, sST2 was not associated with the risk of non-fatal myocardial infarction [HR 0.68 (95% CI 0.41–1.12); $P = .132$] or non-fatal stroke [HR 1.28 (95% CI 0.64–2.53); $P = .485$].

Conclusions. In HD patients with diabetes mellitus, high concentrations of sST2 were strongly and independently associated with an increased risk of all-cause mortality, CV mortality and death due to infection but not non-fatal CV events.

GRAPHICAL ABSTRACT



Keywords: biomarker, cardiovascular, diabetes mellitus, dialysis, sepsis

INTRODUCTION

In end-stage kidney disease (ESKD), the annual mortality is ~20% and is even higher in haemodialysis (HD) patients with concomitant type 2 diabetes mellitus [1]. In particular, cardiovascular (CV) causes account for about half of all deaths, with sudden cardiac death (SCD) as the most frequent cause, whereas fatal myocardial infarction (MI) and stroke are less common [1, 2]. ESKD patients also carry a high risk of death due to infections, which constitutes the most prevalent non-CV cause of death.

Biomarkers provide a useful tool to estimate prognosis, allowing identification of those patients at highest risk. Suppression of tumorigenesis 2 (ST2) is a member of the interleukin-1 (IL-1) receptor family and exists as a membrane-bound (ST2L) and a soluble (sST2) isoform [3]. IL-33 is the natural ligand to ST2. IL-33/ST2L signalling has several biological functions, both in the CV [4] and immune system [5]. ST2 is not attached to the cell membrane and avidly binds IL-33 and thereby functions as a decoy receptor by disrupting IL-33/ST2L signalling. Over the last decade, circulating levels of sST2 have emerged as a power-

ful prognostic biomarker, particularly in patients with acute and chronic heart failure [6, 7], but also in ischaemic heart disease [8, 9] and MI [10, 11], pulmonary hypertension [12] and chronic kidney disease (CKD) [13].

We measured sST2 concentrations in 1196 participants of the German Diabetes Dialysis Study (4D) [2]. All study participants had type 2 diabetes mellitus and were on maintenance HD for ESKD. We analysed the association of sST2 with all-cause and disease-specific mortality risk and non-fatal CV event risk.

MATERIALS AND METHODS

Study design and participants

The 4D Study has previously been reported in detail [2]. Briefly, the 4D study was a prospective randomized controlled trial among 1255 patients with type 2 diabetes mellitus, ages 18–80 years, on maintenance HD for <2 years. Between March 1998 and October 2002, patients were recruited in 178 dialysis centres in Germany. After a period of 4 weeks, patients

Table 1. Baseline characteristics of patients stratified by quartiles of sST2 concentrations (Q1–Q4)

Characteristics	sST2			
	Q1 (n = 299) (<20.1 ng/mL)	Q2 (n = 299) (20.1–24.9 ng/mL)	Q3 (n = 299) (25.0–32.6 ng/mL)	Q4 (n = 299) (>32.6 ng/mL)
Age (years)	65.8 (8.9)	66 (8.2)	66 (8.1)	67 (8.0)
Male gender, n (%)	127 (42)	152 (51)	177 (59)	193 (65)
Ever smoking, n (%)	106 (35)	118 (39)	125 (42)	139 (46)
BMI (kg/m ²)	28.3 (4.9)	28.0 (4.8)	28 (5)	26 (4.4)
Systolic blood pressure (mmHg)	145 (22)	146 (21)	144 (22)	147 (21)
Diastolic blood pressure (mmHg)	76 (10)	75 (10)	76 (12)	76 (11)
Comorbidities, n (%)				
Arterial hypertension	266 (89)	268 (90)	267 (89)	263 (88)
Arrhythmia	39 (13)	58 (19)	48 (16)	77 (26)
Peripheral vascular disease	122 (41)	145 (48)	122 (41)	153 (51)
Ischaemic heart disease	79 (26)	88 (29)	87 (29)	99 (33)
Chronic heart failure	82 (27)	114 (38)	99 (33)	131 (44)
Haemoglobin (g/dL)	10.9 (1.3)	11.0 (1.4)	11.0 (1.4)	11 (1.4)
Haemoglobin A1c (%)	6.6 (1.2)	6.7 (1.3)	6.7 (1.3)	6.9 (1.4)
Potassium (mmol/L)	5.3 (0.8)	5.2 (0.9)	5.2 (0.8)	5.0 (0.8)
Phosphate (mmol/L)	6.0 (1.5)	5.9 (1.5)	6.1 (1.5)	6.2 (1.8)
Albumin (g/dL)	3.8 (0.3)	3.8 (0.3)	3.8 (0.3)	3.8 (0.3)
C-reactive protein (mg/L), median (IQR)	3.6 (7.0)	5.2 (9.4)	5.1 (10.0)	6.4 (13.6)
NT-proBNP (pg/mL), median (IQR)	2245 (5199)	2958 (5044)	3217 (6659)	5928 (14 470)
Troponin T (ng/L), median (IQR)	0.04 (0.06)	0.05 (0.06)	0.06 (0.07)	0.07 (0.09)
Cholesterol (mg/dL)	218 (41)	224 (45)	223 (41)	212 (43)
Duration of diabetes (years)	17.6 (8.8)	18.4 (8.9)	17.9 (8.2)	18.5 (8.2)
Dialysis duration (months)	8.2 (7.1)	8.3 (7.0)	7.8 (6.3)	8.7 (7.0)

Values are presented as mean (SD) unless stated otherwise.

were randomly assigned to double-blinded treatment with either 20 mg of atorvastatin ($n = 619$) or placebo ($n = 636$) once daily. Study visits took place three times before randomization (Visits 1–3), at randomization (Visit 4), at 4 weeks (Visit 5) and every 6 months (Visit 6) after randomization until the date of death, censoring or the end of the study in March 2004. The study complied with the Declaration of Helsinki, was approved by the relevant medical ethics committees and all patients gave written informed consent before inclusion.

Outcomes

The primary endpoint of the 4D study was defined as a composite of death from cardiac causes, fatal or non-fatal stroke and non-fatal MI, whichever occurred first (composite CV endpoint). Death from cardiac causes comprised SCD, fatal MI (death within 28 days after MI), death due to heart failure, death due to coronary heart disease during or within 28 days after intervention and all other deaths ascribed to coronary heart disease. SCD was considered as death verified by terminal rhythm disorders in an electrocardiogram (ECG); by witnesses who observed death within 1 h after the onset of cardiac symptoms; confirmed by autopsy; unexpected death, presumably or possibly of cardiac origin and in the absence of a potassium level ≥ 7.5 mmol/L before the start of the three most recent sessions of HD. MI was diagnosed when two of the following three criteria were met: typical symptoms, elevated levels of cardiac enzymes or diagnostic changes on the ECG. A stroke was defined as a neurologic deficit lasting >24 h. Endpoints were centrally adjudicated according to predefined criteria by three members of the endpoint committee blinded to the study.

Data collection

Information on age, gender and smoking status was obtained through patient interviews. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Smoking status was classified as never, former or current. Comorbidities, including the presence of coronary artery disease and congestive heart failure, as well as the duration of diabetes mellitus and dialysis treatment, were reported by the patients' nephrologists. Coronary artery disease was defined by the history of MI, coronary artery bypass grafting surgery, percutaneous coronary intervention and the presence of coronary heart disease, as documented by coronary angiography. Congestive heart failure was defined according to the classification system of the New York Heart Association. Arrhythmias such as atrial fibrillation or atrial flutter were diagnosed according to an ECG. Blood pressure was measured in the sitting position before the start of the dialysis session.

Laboratory analysis

All blood samples were drawn from study participants before the start of the dialysis session and before the administration of drugs. Levels of sST2 were measured in blood samples taken at baseline at study Visit 3 (1 week before randomization) and stored at -80°C . Plasma was available for the current analysis from 1196/1255 patients. sST2 was measured on a fully automated BEP 2000 instrument (Siemens Healthcare Diagnostics, Marburg, Germany) with the Presage ST2 sandwich immunoassay assay (Critical Diagnostics, San Diego, CA, USA); CVs were $<4.0\%$, as previously described [14].

Statistical analysis

We calculated summary statistics of patient characteristics for subpopulations defined by quartiles of sST2 concentrations. The association of sST2 with clinical endpoints was assessed by multivariable Cox regression analyses calculating adjusted hazard ratios (aHRs) with corresponding 95% confidence intervals (CIs). We fitted different Cox models starting with a univariable (unadjusted) model, followed by a model adjusted for age, sex and treatment allocation (atorvastatin medication; multivariable model 1) and a model (multivariable model 2) additionally adjusted for BMI, cholesterol, phosphate, potassium, atrial fibrillation and peripheral vascular disease. In the core models, sST2 concentrations were coded as a four-level categorical variable reflecting the subpopulations defined by quartiles of sST2 concentrations. In addition, we fitted models using a restricted cubic spline transformation of the sST2 concentrations aimed to visualize the risk association pattern as a function of continuous sST2 exposure. For all covariables included in the Cox models, we graphically checked the condition of the proportional hazards by log-log plots. All hypothesis testing was two-sided considering a *P*-value of .05 as statistically significant. All statistical analyses were conducted using the statistical software package Stata (version 13; StataCorp, College Station, TX, USA).

RESULTS

From March 1998 to October 2002, 1255 participants were enrolled in the 4D study. The underlying population for this analysis consisted of 1196 participants. The mean age was 66 years [standard deviation (SD) 8.3] and 54% were male. The median sST2 level was 25.0 ng/mL [interquartile range (IQR) 12.5]. Baseline characteristics of study participants according to quartiles of sST2 concentrations are shown in Table 1. Participants with higher sST2 concentrations were of significantly older age, had a higher BMI and were more likely to be male. Further, the prevalence of peripheral vascular disease, atrial fibrillation and heart failure was higher and they had lower phosphate, higher haemoglobin A1c, higher C-reactive protein (CRP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) and troponin T levels (Table 1). During a mean follow-up period of 4.0 years, 586 (49%) participants died; 258 deaths were attributed to cardiac causes, 153 to SCD, 54 to MI, 40 to heart failure and 121 to infectious causes; 157 participants had a non-fatal MI and 66 had a non-fatal stroke.

Baseline sST2 concentrations were strongly associated with all-cause mortality risk (Figure 1A). By multivariable Cox regression analyses adjusted for possible confounders, participants in the highest quartile of sST2 had a 2-fold higher all-cause mortality risk compared with those in the lowest quartile [aHR 2.06 (95% CI 1.61–2.61); *P* < .001] (Table 2). Almost 45% of all deaths were attributable to cardiac causes, a composite of SCD, fatal MI and death due to heart failure. High sST2 concentrations were strongly associated with the risk of cardiac death (Figure 1B). Participants with sST2 levels in the highest compared with the lowest quartile had a more than 2-fold higher risk of cardiac death [HR 2.29 (95% CI 1.55–3.39); *P* < .001] (Table 2). Continuous modelling of sST2 levels with all-cause mortality risk (Figure 2A) and cardiac mortality risk (Figure 2B) showed a log-linear association over the entire spectrum of sST2 concentrations [HR increase per sST2 unit: all-cause mortality 1.03 (95% CI 1.020–1.032); *P* < .001 and cardiac mortality risk 1.03 (95% CI 1.017–1.034); *P* < .001]. Analysis of the individual components of cardiac

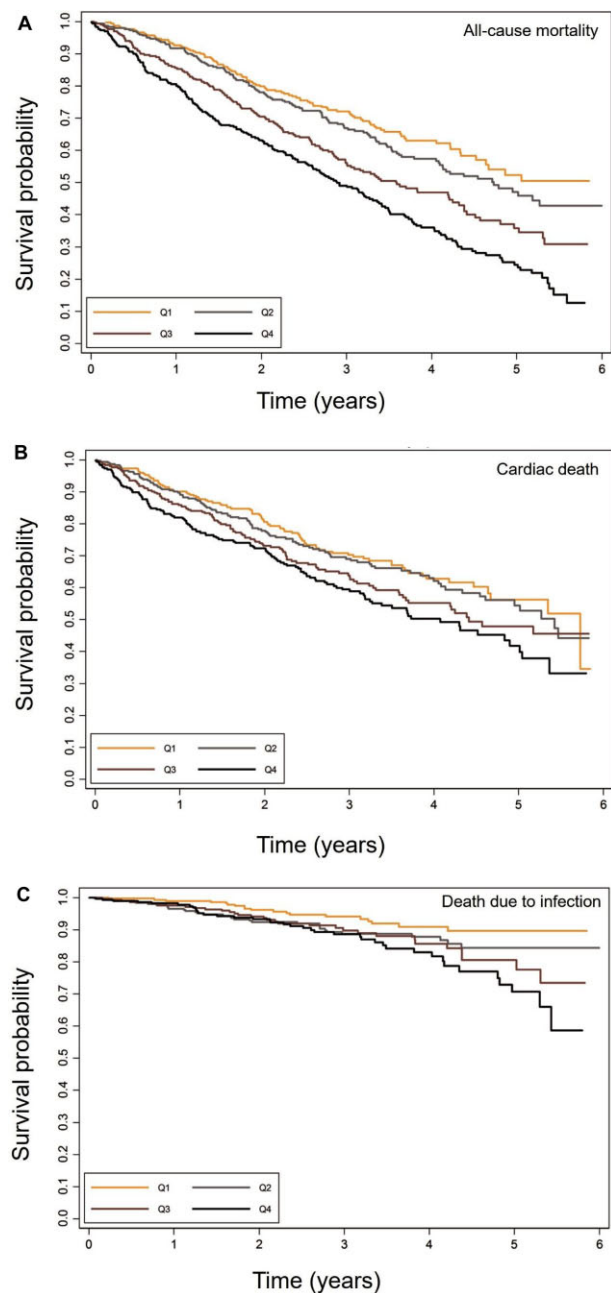


FIGURE 1: Predicted multivariate survival curves adjusted for confounding variables [age, sex, treatment allocation (atorvastatin medication), BMI, cholesterol, phosphate, potassium, atrial fibrillation, peripheral vascular disease] obtained from the Cox regression model: (A) all-cause death, (B) cardiac death and (C) death due to infection according to sST2 quartiles.

causes of death showed similar strong associations with sST2 concentrations: participants in the highest quartile of sST2 concentrations had a >2-fold increased risk of dying from SCD [aHR 2.24 (95% CI 1.33–3.77); *P* = .002], a more than doubled risk of dying from MI [aHR 2.12 (95% CI 0.90–5.00); *P* = .087] and a >3-fold increased risk of dying from heart failure [aHR 3.34 (95% CI 1.15–9.75); *P* = .027] compared with participants in the lowest quartile (Table 2). Besides cardiac causes of death, higher sST2 levels were also associated with an increased risk of fatal stroke [aHR 1.92 (95% CI 1.17–3.14), *P* = .009]. In contrast to fatal CV events, sST2 showed

Table 2. Univariable and multivariable HRs with 95% CIs for all-cause mortality, cardiac death, death due to heart failure, sudden cardiac death, fatal MI, fatal stroke and death due to infection of subpopulations defined by quartiles (Q) of sST2 concentrations

	sST2						
	Q1	Q2		Q3	Q4		P-value (versus Q1)
	(<20.1 ng/mL)	(20.1–25 ng/mL)		(25.1–32.6 ng/mL)	(>32.6 ng/mL)		
HR (95% CI)	HR (95% CI) (versus Q1)	P-value (versus Q1)	HR (95% CI) (versus Q1)	P-value (versus Q1)	HR (95% CI) (versus Q1)	P-value (versus Q1)	
All-cause mortality (n = 586)							
Univariable	1	1.18 (0.91–1.52)	.205	1.65 (1.25–2.18)	<.001	2.27 (1.79–2.90)	<.001
Model 1	1	1.17 (0.91–1.51)	.225	1.62 (1.24–2.13)	.001	2.27 (1.77–2.91)	<.001
Model 2	1	1.12 (0.87–1.45)	.371	1.64 (1.25–2.16)	<.001	2.06 (1.61–2.61)	<.001
Cardiac death (n = 258)							
Univariable	1	1.35 (0.88–2.06)	.172	1.87 (1.23–2.85)	.004	2.62 (1.78–3.85)	.001
Model 1	1	1.34 (0.87–2.06)	.188	1.85 (1.20–2.84)	.005	2.60 (1.73–3.90)	.001
Model 2	1	1.26 (0.83–1.91)	.282	1.87 (1.55–3.39)	.001	2.29 (1.55–3.39)	.001
Sudden cardiac death (n = 153)							
Univariable	1	1.43 (0.85–2.41)	.175	1.85 (1.11–3.10)	.019	2.33 (1.41–3.87)	.001
Model 1	1	1.46 (0.87–2.46)	.151	1.94 (1.14–3.28)	.014	2.50 (1.48–4.23)	.002
Model 2	1	1.35 (0.80–2.29)	.259	2.00 (1.18–3.38)	.010	2.24 (1.33–3.77)	.002
Fatal myocardial infarction (n = 54)							
Univariable	1	1.39 (0.61–3.17)	.439	1.51 (0.69–3.30)	.301	2.61 (1.17–5.80)	.019
Model 1	1	1.35 (0.64–3.16)	.495	1.42 (0.64–3.16)	.387	2.42 (1.05–5.58)	.038
Model 2	1	1.26 (0.53–2.98)	.607	1.34 (0.59–3.05)	.482	2.12 (0.90–5.00)	.087
Death due to heart failure (n = 40)							
Univariable	1	1.22 (0.33–4.46)	.769	3.64 (1.21–10.94)	.021	5.19 (1.82–14.85)	.002
Model 1	1	1.12 (0.30–4.15)	.867	3.12 (1.04–9.29)	.042	4.26 (1.48–12.28)	.007
Model 2	1	1.03 (0.30–3.56)	.958	3.02 (1.06–8.61)	.038	3.34 (1.15–9.75)	.027
Fatal stroke (n = 94)							
Univariable	1	0.70 (0.37–1.32)	.266	1.30 (0.72–2.34)	.379	1.57 (0.97–2.55)	.066
Model 1	1	0.72 (0.38–1.37)	.318	1.46 (0.82–2.60)	.195	1.88 (1.15–3.06)	.011
Model 2	1	0.72 (0.39–1.33)	.291	1.51 (0.85–2.69)	.162	1.92 (1.17–3.14)	.009
Death due to infection (n = 121)							
Univariable	1	1.60 (0.86–2.99)	.138	1.85 (0.99–3.44)	.052	2.43 (1.41–4.20)	.001
Model 1	1	1.56 (0.84–2.91)	.159	1.75 (0.94–3.28)	.008	2.31 (1.35–3.95)	.002
Model 2	1	1.50 (0.80–2.83)	.209	1.70 (0.91–3.17)	.097	2.01 (1.20–3.37)	.008

Model 1: adjustments for age, sex and treatment allocation (atorvastatin medication); Model 2: adjustments for age, sex, treatment allocation (atorvastatin medication), BMI, cholesterol, phosphate, potassium, atrial fibrillation and peripheral vascular disease.

no association with non-fatal MI [aHR 0.68 (95% CI 0.41–1.12); $P = .132$] or non-fatal stroke [aHR 1.28 (95% CI 0.64–2.53); $P = .485$].

Fatalities due to infection accounted for ~20% of all deaths and showed similarly strong associations with sST2 levels (Figure 1C). Participants in the highest sST2 quartile had a doubled risk of dying from infection [aHR 2.01 (95% CI 1.20–3.14); $P = .008$] compared with those in the lowest quartile (Table 2).

To test if the associations of sST2 and outcomes were linked to one of three potentially underlying mechanistic pathways of diseases, namely inflammation, heart failure and cardiac ischaemia, we extended the adjustments in the multivariable Cox regression analysis by CRP (inflammation), diagnosis of heart failure and concentrations of NT-proBNP (heart failure) and diagnosis of coronary artery disease and troponin T (cardiac ischaemia), respectively. However, these adjustments did not materially affect the associations of sST2 levels with cause-specific mortality risk (Table 3).

DISCUSSION

We identified sST2 as an independent prognostic marker of fatal but not non-fatal events in participants of the 4D study who had type 2 diabetes mellitus and were on maintenance HD

treatment. Higher levels of sST2 were associated with all-cause mortality as well as cause-specific mortality risk, including SCD, MI, heart failure, stroke and death due to infections. Importantly, extensive adjustments for potential confounders including established biomarkers of CV disease and comorbidities did not materially affect these associations.

The association of high sST2 levels with increased morbidity and mortality risk has been reported for several CV disease entities in non-ESKD patients. High levels of sST2 have been linked with increased mortality risk in acute [15, 16] and chronic heart failure [6, 7]. This association has been shown to be independent of established biomarkers of CV risk such as NT-proBNP and high-sensitivity troponin T [17]. In stable coronary artery disease patients, sST2 predicted long-term all-cause mortality [8] and sudden cardiac death [18], whereas acute MI-elevated sST2 levels were associated with adverse cardiac remodelling [19] and increased risk of CV death, heart failure [11] and short-term survival [10].

More recently the relationship between sST2 and mortality risk was investigated in two reasonably sized HD cohorts. Zhang et al. [20] reported a 1.31 relative risk ratio per 1 SD increase of log-transformed sST2 for all-cause mortality risk and a 2.1 relative risk ratio for CV mortality risk after adjusting for

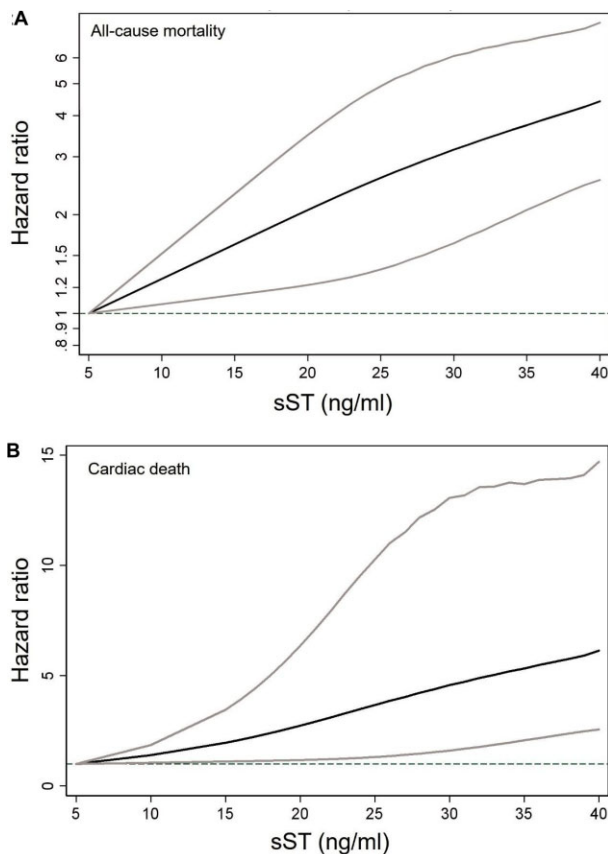


FIGURE 2: Unadjusted restricted cubic spline analysis for the association of sST2 levels with (A) all-cause mortality risk and (B) cardiac death risk showing a log-linear relationship.

NT-proBNP and troponin T in 414 HD patients. Obokata et al. [21] reported an almost 4-fold increase in all-cause mortality risk in 423 HD patients in the high compared with the low sST2 tertile, which was independent of galectin-3 and NT-proBNP. Similar associations of sST2 and mortality risk have also been reported in smaller HD cohorts [13].

Our study differs from and expands upon these reports in several ways: we were able to analyse cause-specific mortality and non-fatal CV events. Further, our study is the largest with the longest follow-up time and centrally adjudicated events according to prespecified criteria. In contrast to previous studies, where the prevalence of diabetes mellitus was reported between 23 and 46% [20–23], all participants of this study had type 2 diabetes [2]. Published data on the effect of diabetes on sST2 levels are inconsistent: in the general population and in patients with heart failure with preserved ejection fraction, the presence of diabetes was associated with higher sST2 levels [24, 25], whereas no difference was reported in heart failure with reduced ejection fraction [26]. In a cohort of HD patients with a rather low prevalence of diabetes of 23%, the median sST2 concentration was 26.9 ng/mL, which is almost identical to our study [20].

Besides its association with all-cause mortality risk, we were able to detect a consistent 2- to 3-fold increase in the risk for SCD, fatal MI, death due to heart failure and fatal stroke in patients with high sST2 levels. These associations were not materially affected after adjusting for established CV biomarkers including troponin T and NT-proBNP and are similar to findings in non-ESKD patients with stable CV disease [6–8,

18]. The association of adverse outcomes and sST2 levels was independent of known confounders, which we controlled for in the multivariable analysis.

Although sST2 was initially identified to be induced by mechanical strain in rat cardiomyocytes [27], studies in human cardiac tissue predominantly located the expression of its transmembrane (ST2L) and its soluble form (sST2) in endothelial cells, whereas cardiomyocytes and fibroblasts were the main sources of IL-33 [28]. Results from experimental studies showed that IL-33/ST2L signalling has protective CV effects, whereas its disruption resulted in adverse cardiac remodelling by aggravating cardiac hypertrophy and fibrosis in models of heart failure and MI [29–32]. Administration of IL-33 in an animal model of atherosclerosis resulted in a profound reduction in atherosclerotic plaque size due to a decreased accumulation of macrophage-derived foam cells in the aortic sinus, whereas inhibition of IL-33 signalling had opposite effects [33, 34]. These studies provide pathophysiological insights into how sST2 may modulate the clinical course of CV disease by disrupting IL-33/ST2L signalling and allow the notion that sST2 in the circulation may be a surrogate of disrupted IL-33/ST2L signalling in the CV system that results in an adverse outcome. However, in contrast to fatal events, higher sST2 levels were not associated with an increased risk in non-fatal CV events in this study. Although surprising, similar observations have been reported in the general population [35, 36] and in other disease entities such as stable coronary artery disease [9] and CKD [37], where sST2 predicted (CV) mortality but not non-fatal CV events. In summary, and in contrast to experimental studies, data from clinical studies do not support the notion that sST2 accelerates atherosclerotic disease and thereby, increases the risk of CV events as such but, importantly, adversely impacts survival following such events.

Apart from CV events, we showed sST2 to be a strong predictor of death due to infection, which constitutes the second most frequent cause of death in HD patients. In non-ESKD patients, high sST2 concentrations have been associated with increased mortality risk in sepsis patients [38, 39]. IL-33 has been shown to orchestrate complex innate and adaptive immune responses [40] and in an experimental sepsis model, administration of IL-33 facilitated neutrophil recruitment and bacterial clearance, suggesting a beneficial role of IL-33/ST2L signalling in bacterial infections [41, 42].

Given that sST2 levels are not affected by dialysis [43] and have a low intra-individual variation [44], sST2 in comparison with NT-proBNP has ideal characteristics as a prognostic biomarker in ESKD patients. Concentrations of sST2 were not particularly high in this study compared with the general population [35, 36]. In fact, 80% of participants had an sST2 concentration within the reference range of the assay (<35 ng/mL), which is in good agreement with previous reports in ESKD patients [21, 43]. However, the prediction of adverse outcomes was not restricted to elevated sST2 levels per se, as we detected a log-linear association of mortality risk over the entire spectrum of sST2 concentrations.

In contrast to heart failure patients, where reductions in sST2 have been established as an indicator of improved outcome [45, 46], the prognostic value of a reduction in sST2 in ESKD has not been investigated so far. Although higher sST2 concentrations are independently associated with increased mortality risk in ESKD patients, the benefit of sST2 measurements in routine clinical practice for individual patients remains to be established, given the lack of a clinical prediction model or the prognostic relevance of serial sST2 measurements [47].

Table 3. Sensitivity analysis to investigate the contribution of three potentially underlying pathophysiological pathways (inflammation, heart failure and cardiac ischaemia) on HRs (highest versus lowest sST2 quartile subgroup) with 95% CIs and outcome

	sST2		
	Q1 (<20.1 ng/mL)	Q4 (>32.6 ng/mL)	
	HR (95% CI)	HR (95% CI) versus Q1	P-value versus Q1
All-cause mortality (core estimate)	1	2.06 (1.61–2.61)	<.001
+ adj. for inflammation	1	1.87 (1.48–2.37)	<.001
+ adj. for heart failure	1	1.81 (1.42–2.30)	<.001
+ adj. for cardiac ischaemia	1	1.98 (1.55–2.54)	<.001
Cardiac Death	1	2.29 (1.55–3.39)	.001
+ adj. for inflammation	1	2.12 (1.42–3.17)	.001
+ adj. for heart failure	1	2.03 (1.37–3.02)	.001
+ adj. for cardiac ischaemia	1	2.26 (1.51–3.38)	.001
Sudden cardiac death	1	2.24 (1.33–3.77)	.002
+ adj. for inflammation	1	2.05 (1.20–3.51)	.009
+ adj. for heart failure	1	1.94 (1.13–3.33)	.017
+ adj. for cardiac ischaemia	1	2.34 (1.40–3.92)	.001
Fatal myocardial infarction	1	2.12 (0.90–5.00)	.087
+ adj. for inflammation	1	2.03 (0.85–4.82)	.066
+ adj. for heart failure	1	2.09 (0.88–4.97)	.094
+ adj. for cardiac ischaemia	1	2.00 (0.83–4.80)	.123
Death due to heart failure	1	3.34 (1.15–9.75)	.027
+ adj. for inflammation	1	2.82 (0.97–8.18)	.056
+ adj. for heart failure	1	2.95 (1.05–8.32)	.041
+ adj. for cardiac ischaemia	1	2.91 (0.97–8.77)	.058
Fatal stroke	1	1.92 (1.17–3.14)	.009
+ adj. for inflammation	1	2.01 (0.97–4.17)	.062
+ adj. for heart failure	1	2.04 (0.91–4.55)	.084
+ adj. for cardiac ischaemia	1	2.01 (0.97–4.17)	.007
Death due to infection	1	2.01 (1.20–3.37)	.008
+ adj. for inflammation	1	1.72 (1.03–2.90)	.040
+ adj. for heart failure	1	1.70 (0.99–2.91)	.053
+ adj. for cardiac ischaemia	1	1.90 (1.12–3.23)	.018

Core estimates refer to Model 2 adjusted for age, sex, treatment allocation (atorvastatin medication), BMI, cholesterol, phosphate, potassium, atrial fibrillation and peripheral vascular disease. Additional adjustments (adj.) for the following models were inflammation: C-reactive protein; heart failure: diagnosis of chronic heart failure and levels of BNP; ischaemic heart disease: diagnosis of coronary artery disease and troponin T levels.

In summary, we found sST2 to be a strong and independent predictor of fatal events in a large cohort of HD patients with type 2 diabetes mellitus. The prognostic utility was not only related to CV causes of death, but also to death due to infection, whereas sST2 concentrations did not predict non-fatal CV events.

Strengths and limitations

Strengths of our study are the large number of participants, the prospective study design, central adjudication of outcome measures according to pre specified criteria and the long period of follow-up. Limitations include that this was a post hoc analysis of a selected cohort of German HD patients with type 2 diabetes mellitus and thus the relationship between sST2 and increased mortality risk may not be generalizable to other patient populations. Despite the extensive adjustments for several confounding factors, residual confounding cannot be excluded. Finally, causality cannot be deduced from observational data.

CONFLICT OF INTEREST STATEMENT

The results presented in this work have not been published previously in whole or part, except in abstract format. F.H. reports grants from the German Ministry for Education and Research and speaker honoraria/consultation fees from Novartis, Daiichi Sankyo and Vifor. S.S. reports grants from the German Ministry for Education and Research, research grants from Bayer and Boehringer and speaker honoraria/consultation fees from AstraZeneca, Bayer, Boehringer Ingelheim, Novartis, Pfizer, Sanofi and Servier, all outside the submitted work. C.W. is member of the CKJ editorial board. C.W. received grant support and honoraria outside of the present trial from Boehringer Ingelheim, Idorsia and Sanofi-Genzyme and honoraria from AstraZeneca, Bayer, Chiesi, FMC, Gilead, GlaxoSmithKline, Eli Lilly, MSD and Vifor. B.G., B.D., M.E., T.M., C.D., W.M. and V.K. have nothing to disclose.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared upon reasonable request to the corresponding author.

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