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The modulating effect of circulating carbohydrate antigen 125 on ST2 and long-term recurrent morbidity burden

Elena Revuelta-López[1,2,4], Rafael de la Espriella[2,3,4], Gema Miñana[3], Enrique Santas[3], Sandra Villar[3], Juan Sanchis[2,3], Antoni Bayés-Genís[1,2] & Julio Núñez[2,3]✉

Soluble ST2 (sST2) is released in response to vascular congestion, inflammation, and pro-fibrotic stimuli. In heart failure (HF), elevated levels of sST2 are associated with a higher risk of adverse clinical outcomes. Emerging evidence suggests that carbohydrate antigen 125 (CA125) may act as a ligand that modulates the inflammatory response. We hypothesized that CA125 might be modulating sST2 activity. In a cohort of 160 patients with acute (AHF) and renal dysfunction, we investigated whether the prognostic value of sST2 varies according to CA125 levels. The endpoints were: (a) total cardiovascular and renal hospitalizations and (b) all-cause mortality during follow-up. Cox regression analyses assessed the association between admission sST2 and endpoints across CA125 (≤ 35 vs. > 35 U/ml). This sub-study of the IMPROVE-HF trial shows that sST2 predicted the composite of cardiovascular or renal rehospitalizations when CA125 was elevated (> 35 U/ml) but not when CA125 ≤ 35 U/ml. These results highlight a potential biological interaction between sST2 and CA125, suggesting that CA125 status may refine the prognostic utility of sST2 in AHF. Clinically, these insights could guide personalized risk stratification and management strategies in this high-risk population.

Keywords CA125, Heart failure, Inflammatory modulator, sST2

Background

Acute heart failure (AHF) is a complex syndrome commonly accompanied by renal dysfunction and related to high mortality and hospital readmissions. AHF is associated with systemic inflammation, where soluble ST2 (sST2), a surrogate of inflammations and fibrosis[1], provides prognostic information[2]. In AHF syndromes, elevated sST2 plasma values are related to disease severity, poor diuretic response, and increased cardiovascular death[3,4].

Carbohydrate antigen 125 (CA125) has also shown value as a congestion and inflammation biomarker in AHF[5,6]. Recent data suggest CA125 may play a relevant role as a ligand[7], modulating inflammatory response by interacting with several molecules[8]. For instance, current evidence identified CA125 as a specific binding partner of soluble lectins, including galectin-1 and − 3[9]. Through specific interactions with glycosylated proteins, galectins modify their biological activity[10]. In this regard, in AHF, a prior study showed that the association between galectin-3 and adverse clinical endpoints was influenced by CA125 levels, which higher galectin-3 were deleterious in patients with higher CA125 values and not in the rest[11].

CA125 is highly correlated with clinical signs of congestion and fluid accumulation[5], while sST2 reflects tissue damage related to mechanical stress[12]. This indirect interaction suggests that both CA125 and sST2 could be expressed in response to mechanical and inflammatory overloads, exacerbating each other. Although there is no direct evidence of molecular interaction between these biomarkers, their roles in shared inflammatory and fibrotic pathways may be related, especially in the context of decompensated HF. The structure of CA125 (also known as MUC16), with a highly glycosylated extracellular domain, makes its interaction with other proteins viable, allowing it to function as a modulator in several biological processes[13]. In the other hand, sST2 contains

[1]Cardiology Department, Hospital Universitari Germans Trias i Pujol, Universitat Autònoma de Barcelona, Badalona, Barcelona, Spain. [2]CIBER Cardiovascular, Madrid, Spain. [3]Cardiology Department, Hospital Clínico Universitario, INCLIVA. Universitat de València, Valencia, Spain. [4]Elena Revuelta-López and Rafael de la Espriella have contributed equally. ✉email: yulnunez@gmail.com

an immunoglobulin-like domain (Ig-like) in its extracellular region, which is structurally flexible and gives it the potential to interact with proteins beyond its native IL-33 receptor[14].

Accordingly, we hypothesize that there could be a direct interaction between CA125 and sST2, in this way CA125 might modify the association between sST2 and adverse clinical events in patients with AHF. We therefore explored the prognostic effect of sST2 across CA125 in patients with AHF and renal dysfunction.

Methods

Study sample

This is a post-hoc analysis of a multicentre, open-label, randomized clinical trial (IMPROVE-HF) (ClinicalTrials.gov NCT02643147) that randomized 160 patients with AHF and renal dysfunction on admission to (a) the standard diuretic strategy, or (b) a carbohydrate antigen 125-guided diuretic strategy. The design and main findings were published elsewhere[15]. The study was approved by local ethics committee and conformed to the principles of the Helsinki Declaration. All patients provided signed informed consent and the protocol was approved by the research ethics committee of Hospital Clínico Universitario de Valencia.

CA125 and sST2 were measured using standard commercial enzyme immune analysis (Roche Elecsys® CA 125 assay and Critical Diagnostics Presage® ST2 assay).

Endpoints

The endpoints were: (a) total cardiovascular and renal hospitalizations and (b) all-cause mortality during follow-up. Cardiovascular and renal hospitalizations encompassed those attributed to worsening HF, acute myocardial infarction, stroke or transient ischemic attack, cardiac arrhythmias, peripheral artery disease, and renal causes (worsening renal function, end-stage renal failure, and dialysis). HF readmission was defined as an unscheduled hospital stay lasting more than 24 h, during which the patient required parenteral diuretics or vasoactive drugs. The assessment of mortality outcomes was performed by verifying the patient's survival status at each hospitalization, and office visit or by reviewing electronic medical records.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median [interquartile range (IQR)] when appropriate. sST2 and CA125 were categorized according to accepted threshold levels (sST2: ≤35 vs. >35 ng/ml and CA125: ≤35 vs. >35 U/ml). Differences among sST2 and CA125 groups were tested with ANOVA or Kruskal-Wallis rank test, as appropriate. Discrete variables were presented as percentages and compared with the χ^2 test. Mortality and rehospitalizations rates were reported as the number of events per 10 person-years (P-Y). To consider the positive relationship between rehospitalizations and mortality, we employed the Famoye bivariate Poisson regression model.

The final model for rehospitalizations and mortality endpoints included age, sex, prior admission, systolic blood pressure, heart rate, estimated GFR, hemoglobin, NT-proBNP, LVEF, and treatment allocation (usual care vs. diuretic CA125-guided therapy) (Selection based on subject-matter expertise and regardless of the p-value). A bilateral p-value of < 0.05 was set as the threshold for statistical significance. All analyses were performed with STATA 16.1 [Stata Statistical Software, Release 16 (2019); StataCorp LP, College Station, TX, USA].

Results

The baseline and biomarker characteristics of the total cohort are detailed in Table 1. The mean ± SD age of the sample was 77.9 ± 7.9 years, and 107 (66.9%) were men. The proportion of patients with LVEF < 40%, 41–49%, and ≥ 50% were 37.5%, 9.4%, and 53.1%, respectively. The mean eGFR at presentation was 34.0 ± 8.5 ml/min/1.73m^2. The median (p25-p75%) of NT-proBNP, sST2, and CA125 were 7765 pg/ml (3525–15369), 67.9 ng/mL (44.5-122.6), and 57.5 U/ml (22.6–11.9), respectively. The proportion of patients with low values of CA125 was 35.6% (Table 2).

ACE-I Angiotensin-converting enzyme inhibitor; ARB Angiotensin II receptor blocker; eGFR estimated glomerular filtration rate; DBP; Diastolic blood pressure; LVEF, Left ventricular ejection fraction; MRA, Mineralcorticoids; NT-proBNP, N-terminal pro b-type natriuretic peptide; SBP, Systolic blood pressure.

ACE-I Angiotensin-converting enzyme inhibitor; ARB Angiotensin II receptor blocker; eGFR estimated glomerular filtration rate; DBP; Diastolic blood pressure; LVEF, Left ventricular ejection fraction; MRA, Mineralcorticoids; NT-proBNP, N-terminal pro b-type natriuretic peptide; SBP, Systolic blood pressure.

Patients with sST2 > 35 ng/mL and CA125 > 35 U/ml were 136 (85%) and 103 (64.4%). The correlation between sST2 and CA125 was positive (Spearman correlation $r = 0.25$, $p = 0.002$). Baseline characteristics across sST2-CA125 groups are shown in Table 3. Patients with both biomarkers elevated (sST2 > 35 ng/mL and CA125 > 35 U/ml) were 91 (56.9%). These patients showed higher rates of III/IV peripheral edemas and higher NT-proBNP and were treated with a more intensive furosemide regime (Table 3).

sST2 and adverse clinical events

At a median (p25% to p75%) follow-up of 1.73 years (0.48-2,25), 83 (51.9%) deaths, 267 cardiovascular-renal (CV-renal) hospitalizations in 110 (68.8%) patients (1.48 per 10 P-Y), and 160 HF-rehospitalizations in 81 patients (14.8 per 10 P-Y), were registered. In the whole sample, patients with sST2 > 35 ng/mL identified patients with higher rates of CV-renal (15.3 vs. 11.8 × 10 P-Y, $p = 0.013$) and HF-rehospitalizations (8.8 vs. 7.0 × 10 P-Y, $p = 0.022$) but not with higher rates of death (3.4 vs. 2.7 × 10 P-Y, $p = 0.483$). The rates of CV-renal and HF-hospitalizations (x 10 P-Y) were higher in patients with sST2 > 35 ng/mL when CA125 was > 35 U/ml (19.0 vs. 10.3, $p = 0.031$, and 9.1 vs. 5.0, $p = 0.049$, respectively) but not when CA125 ≤ 35 U/ml (8.0 vs. 12.2, $p = 0.263$ and

	Total ($n=160$)
Age, years	77.9 ± 7.9
Male, n (%)	107 (67)
Weight, kg	77 ± 14
Hypertension, n (%)	144 (90)
Diabetes mellitus, n (%)	90 (56.3)
Sodium, mEq/l	139 ± 4.5
Hemoglobin, g/dl	11.7 ± 1.9
eGFR, ml/min/1.73m^{2}*	33.3 (28.6–39.6)
HF etiology Ischemic, n (%) Valvular, n (%) Others, n (%)	 53 (34) 39 (25) 65 (41)
Previous Renal dysfunction, n (%)	106 (66)
LVEF, %	47.5 ± 14.5
Heart rate, bmp	75.4 ± 17.7
SBP, mmHg	127.3 ± 23.3
DBP, mmHg	67.1 ± 13.1
CA125-guided therapy, n (%)	79 (49)
Pulmonar rales, n (%)	112 (70)
Jugular engorment, n (%)	71 (44.4)
Peripheral edema Absence, n (%) I/II, n (%) III/IV, n (%)	 33 (20.6) 74 (46.3) 53 (33.1)
Accumulated 72 h-dose Furosemide equivalent (mg/24 h)*	380 (245–640)
Treatment ACE-I or ARB, n (%) β-Blocker n (%) MRA n (%) Statins n (%) Aldosterone n (%)	 77 (48) 116 (73) 64 (40) 112 (70) 56 (35)

Table 1. Baseline and biomarker characteristics of total cohort. *Data given as n (%), mean ± standard deviation or median (P25 to P75).

7.1 vs. 9.8, $p=0.521$). The rates of death (x 10 P-Y) attributable to sST2 > 35 ng/mL did not significantly differ across CA125 status [3.8 vs. 1.8 ($p=0.163$) if CA125 > 35 U/ml and 2.7 vs. 3.8 ($p=0.483$) if CA125 ≤ 35 U/ml].

After multivariate adjustment, in the whole sample, higher sST2 was not associated with a higher risk of CV-renal ($p=0.090$), HF events ($p=0.267$), and mortality ($p=0.397$). Further adjusted analysis revealed that the associations between sST2 (along the continuum) and CV-renal rehospitalizations were significantly modulated by CA125 status (interaction p-value = 0.041) (Fig. 1A and B). In patients with CA125 > 35 U/ml, sST2 was positive and significantly associated with an increased risk of CV-renal hospitalizations ($p=0.027$), as shown in Fig. 1B. On the contrary, sST2 was not related to the endpoint when CA125 ≤ 35 U/ml ($p=0.324$), as is depicted in Fig. 1A. Under the same multivariate setting, we did not find statistical evidence of a heterogeneous association between sST2 and HF rehospitalizations ($p=0.127$) and total mortality according to CA125 (interaction $p=0.170$), as is shown in Figs. 2 and 3. However, for these outcomes, there were some numerical signals of higher risk at higher sST2 in subjects with elevated CA125. Covariates risk estimates of the multivariate models are presented in supplementary Tables 1–3. In a sensitivity analysis, forcing in the multivariate model proxies of fluid overload (rales, jugular engorgement, and peripheral edemas) the differential association between sST2 and CV-renal hospitalizations remains (supplementary Fig. 1).

Discussion

This post-hoc analysis of the IMPROVE-HF trial demonstrates that elevated sST2 levels predominantly predict CV-renal rehospitalizations in patients with high CA125 levels (> 35 U/ml), but not in those with CA125 ≤ 35 U/ml. This finding aligns with previous research indicating that the prognostic value of biomarkers such as galectin-3 is significantly influenced by CA125 levels[11]. The interaction between sST2 and CA125 highlights the complex interplay between inflammation and congestion in heart failure, suggesting that CA125 may modulate sST2 activity. The biological mechanisms behind these findings need to be unravelled.

Pathophysiology of MUC16 (CA125)

MUC16 is a large transmembrane mucin with potential cleavage locations[16]. This cleavage allows the release of the N-terminal domain, turning CA125 into a valuable circulating biomarker. Meanwhile, the C-terminal domain (CTD) can stay on the cell surface or translocate to the nucleus, whereas if MUC16 CTD translocates to the nucleus, it acts as a transcriptional co-regulator. In ovarian and pancreatic cancer, MUC16 CTD translocation increases the expression of critical invasion genes, regulating cancer progression[7,17]. Nevertheless, due to its

	CA125 low ($n=57$)	CA125 high ($n=103$)	p-value
Age, years	77.9 ± 7.4	77.9 ± 7.9	0.958
Male, n (%)	33 (57.9)	74 (71.8)	0.073
Weight, kg	75.6 ± 14.1	77.0 ± 14.3	0.088
Hypertension, n (%)	52 (91.2	92 (89.3)	0.700
Diabetes mellitus, n (%)	31 (54.4)	59 (57.3)	0.724
Sodium, mEq/l	138.7 ± 4.5	138.9 ± 4.5	0.455
Hemoglobin, g/dl	11.7 ± 1.9	11.7± 1.9	0.871
eGFR, ml/min/1.73m^2*	32.3 (24.8–37.1)	34.6 (29.7–41.5)	0.031
HF etiology Ischemic, n (%) Valvular, n (%) Others, n (%)	14 (25.0) 14 (25.0) 28 (50.0)	39 (38.6) 25 (24.8) 37 (36.6)	0.171
Previous Renal dysfunction, n (%)	37 (64.9)	69 (67.0)	0.790
LVEF, %	45.4 ± 14.0	47.5 ± 14.5	0.013
Heart rate, bmp	75.5 ± 16.6	75.4 ± 17.7	0.957
SBP, mmHg	123.6 ± 20.8	127.3 ± 23.3	0.007
DBP, mmHg	67.2 ± 14.0	67.1 ± 13.1	0.883
NTproBNP, pg/mL*	4994 (2529–8122)	10,246 (4643–19431)	<0.001
CA125, U/mL*	17.0 (12.0-23-0)	85.0 (59.0-171.4)	<0.001
sST2, ng/mL*	52.6 (37.7–85.3)	82.0 (53.9-146.6)	<0.001
CA125-guided therapy, n (%)	30 (52.6)	49 (47.6)	0.540
Pulmonar rales, n (%)	35 (61.4)	77 (74.8)	0.078
Jugular engorment, n (%)	22 (38.6)	49 (47.6)	0.274
Peripheral edema Absence, n (%) I/II, n (%) III/IV, n (%)	13 (22.8) 31 (54.4) 13 (22.8)	20 (19.4) 43 (41.7) 40 (38.8)	0.115
Accumulated 72 h-dose Furosemide equivalent (mg/24 h) *	260.0 (220.0-320)	520.0 (320.0-810)	<0.001
Treatment ACE-I or ARB, n (%) β-Blocker, n (%) MRA, n (%) Statins, n (%) Aldosterone, n (%)	32 (56.1) 46 (80.7) 18 (31.6) 40 (70)0.2 15 (26.3)	45 (43.7) 70 (68.0) 46 (44.7) 72 (69.9) 41 (39.8)	0.131 0.084 0.106 0.971 0.087

Table 2. Baseline and biomarker characteristics per group of CA125 values. *Data given as n (%), mean ± standard deviation or median (P25 to P75).

structure and glycosylation (O-linked and N-linked) capacity on the cell surface, MUC16 CTD participates in protein-protein interactions that initiate signaling cascades. Recently, it has been described that MUC16 CTD can form an N-glycan-mediated protein binding complex composed of EGFR, β1 integrin and galectin-3 on the cell surface. The formation of these bonds positively regulates the transcription of genes that enhance the epithelial-to-mesenchymal transition (EMT) in ovarian cancer[7]. EMT plays a pivotal role in cancer progression by providing stem cells properties to cancer cells and participates in organ fibrosis and tissue regeneration processes. This process has also been described in pulmonary fibrosis, where TGF-β1 forms a protein complex with MUC16CTD activating EMT in idiopathic pulmonary fibrosis and inducing fibrotic processes[18]. Similarly, recent evidence has demonstrated that MUC16 (CA125) expression in the epicardial fat is associated with markers of inflammation and fibrosis, suggesting a role in myocardial fibrosis. Specifically, MUC16 has been shown to correlate with the expression of fibrotic markers in epicardial fat, indicating that MUC16 may contribute to fibrotic remodeling in the heart through its interactions with these molecular pathways[8].

Literature linked EMT and soluble inflammation mediators, such as TNFα, IL-1β and IL-6[19]. Considering that MUC16 is up-regulated in response to inflammatory stimuli and its levels are correlated with an increase in soluble TNFα, IL-6 and sST2 concentrations in HF patients, an association between systemic inflammation and CA125 status could be suggested[20]. Our study suggests that sST2 is associated to poor clinical outcomes in the context of congestion in HF in patients with concomitantly high CA125 levels. This is in alignment with other clinical studies that describe that (1) severe congestion is associated with up-regulation of sST2 and CA125[21], and (2) hemodynamic congestion and inflammation could be responsible for the upregulation of sST2[22–24]. This highlights the potential interplay between systemic congestion, as reflected by CA125, and the pro-inflammatory pathways involving sST2. The concurrent elevation of both biomarkers may indicate a prolonged and predominant accumulation of pulmonary and systemic tissue volume, accompanied by significant tissue

	sST2 low, CA125 low (*n* = 12)	sST2 high, CA125 low (*n* = 45)	sST2 low, CA125 high (*n* = 12)	sST2 high, CA125 high (*n* = 91)	*p*-value
Age, years	77 ± 11	78 ± 8	78 ± 12	78 ± 7	0.986
Male, n (%)	6 (50)	27 (60)	10 (83)	64 (70)	0.216
Weight, kg	78 ± 16	80 ± 14	79 ± 23	75 ± 13	0.297
Hypertension, n (%)	12 (100)	40 (89)	10 (83	82 (90)	0.575
Diabetes mellitus, n (%)	5 (41)	26 (58)	7 (58)	52 (57)	0.770
Sodium, mEq/l	140 ± 1.5	139 ±4.8	139 ±5.8	139 ± 4.4	0.673
Hemoglobin, g/dl	12.0 ± 2.0	11.6 ± 2.0	12.9 ± 2.0	11.6 ± 1.8	0.123
eGFR, ml/min/1.73m^{2*}	30.1 (23.0–32.0)	35.0 (25.5–39.5)	38.5 (33.9–39.7)	32.9 (29.5–42.4)	0.058
HF etiology Ischemic, n (%) Valvular, n (%) Others, n (%)	2 (17) 4 (33) 6 (50)	12 (27) 10 (23) 22 (50)	4 (40) 0 (0) 6 (60)	35 (39) 25 (28) 31 (34)	0.205
Previous Renal dysfunction, n (%)	6 (50)	31 (69)	6 (50)	63 (69)	0.343
LVEF, %	54.7 ± 10.6	50.4 ± 15.6	42.1 ± 13.8	45.9 ± 14.1	0.051
Heart rate, bmp	78.8 ± 17.9	74.4 ± 20.4	77.7 ±15.8	75.2 ± 16.7	0.848
SBP, mmHg	133.3 ± 20.6	134.0 ± 27.7	123.5 ±19.6	123.6 ± 21.1	0.065
DBP, mmHg	62.7 ± 13.3	68.0 ±10.6	69.8 ±14.	66.9 ± 13.9	0.550
NTproBNP, pg/mL*	2429 (1577–5621)	5481 (3489–9131)	4135 (2590–7859)	11,400 (5308–22885)	< 0.001
CA125, U/mL*	16.9 (9–24)	17.0 (12–23)	117.4 (64–201)	84.4 (58–151)	0.003
sST2, ng/mL*	28.1 (15–32)	62.1 (46–106)	27.4 (8–32)	99.4 (61–164)	< 0.001
CA125-guided therapy, n (%)	6 (50)	24 (53)	4 (3)	45 (50%)	0.678
Pulmonar rales, n (%)	8 (66.7)	27 (60)	8 (66.7)	69 (75.8)	0.291
Jugular engorment, n (%)	6 (50)	16 (35.6)	5 (41.7)	44 (48.4)	0.534
Peripheral edema Absence, n (%) I/II, n (%) III/IV, n (%)	1 (8.3) 9 (75) 2 (16.7)	12 (26.7) 22 (48.9) 11 (24.4)	3 (25.0) 7 (58.3) 2 (16.7)	17 (18.7) 36 (39.6) 38 (41.8)	0.047
Accumulated 72 h-dose Furosemide equivalent (mg/24 h)*	240 (170–270)	260 (240–340)	460 (280–780)	520 (320–810)	< 0.001
Treatment ACE-I or ARB, n (%) β-Blocker, n (%) MRA, n (%) Statins, n (%) Aldosterone, n (%)	5 (42) 11 (92) 4 (33) 10 (83) 3 (25)	27 (60) 35 (78) 14 (31) 30 (67) 12 (27)	6 (50) 8 (67) 6 (50) 8 (67) 6 (50)	39 (43) 62 (68) 40 (44) 64 (70) 35 (39)	0.287 0.271 0.424 0.724 0.312

Table 3. Baseline characteristics per biomarkers (sST2 and CA125) groups. Data given as n (%), mean ± standard deviation or median (P25 to P75) *. ACE-I Angiotensin-converting enzyme inhibitor; ARB Angiotensin II receptor blocker; eGFR estimated glomerular filtration rate; DBP; Diastolic blood pressure; LVEF, Left ventricular ejection fraction; MRA, Mineralcorticoids; NT-proBNP, N-terminal pro b-type natriuretic peptide; SBP, Systolic blood pressure.

inflammation and fibrosis. In contrast, patients with elevated CA125 levels but without a concomitant increase in sST2 tend to exhibit a pathophysiological profile primarily driven by volume overload, but less severe than the high-high group. It should be particularly evident for the lower severity of pulmonary congestion, a tissue where ST2 is predominantly produced in HF[24].

In this sub-study of the IMPROVE-HF trial, elevated sST2 was significantly associated with an increased risk of CV-renal hospitalizations in patients with CA125 > 35 U/ml, but not in those with CA125 ≤ 35 U/ml. Given that sST2 acted as a prognostic biomarker only when CA125 levels were elevated, we propose that CA125 may function as a ligand for sST2, potentially promoting an inflammatory-reparative process through EMT in heart failure, similar to how the TGF-β1-MUC16CTD complex activates EMT in idiopathic pulmonary fibrosis[18] (Fig. 4).

Limitations

Several limitations need to be addressed. First, this is a post-hoc analysis in which several unmeasured confounders may play a role. Second, relatively small sample size. Third, with the current data, we cannot unravel the biological mechanism behind these findings or establish a causal relationship. Fourth, we cannot extrapolate these findings to the whole spectrum of AHF syndromes, especially milder forms of the syndrome. Finally, the influence of novel HF treatments such as SGLT2i and ARNI was not assessed given the low prescription by the time of enrolment and the high proportion of individuals with LVEF > 40% and GFR < 30 ml/min/1.73 m2.

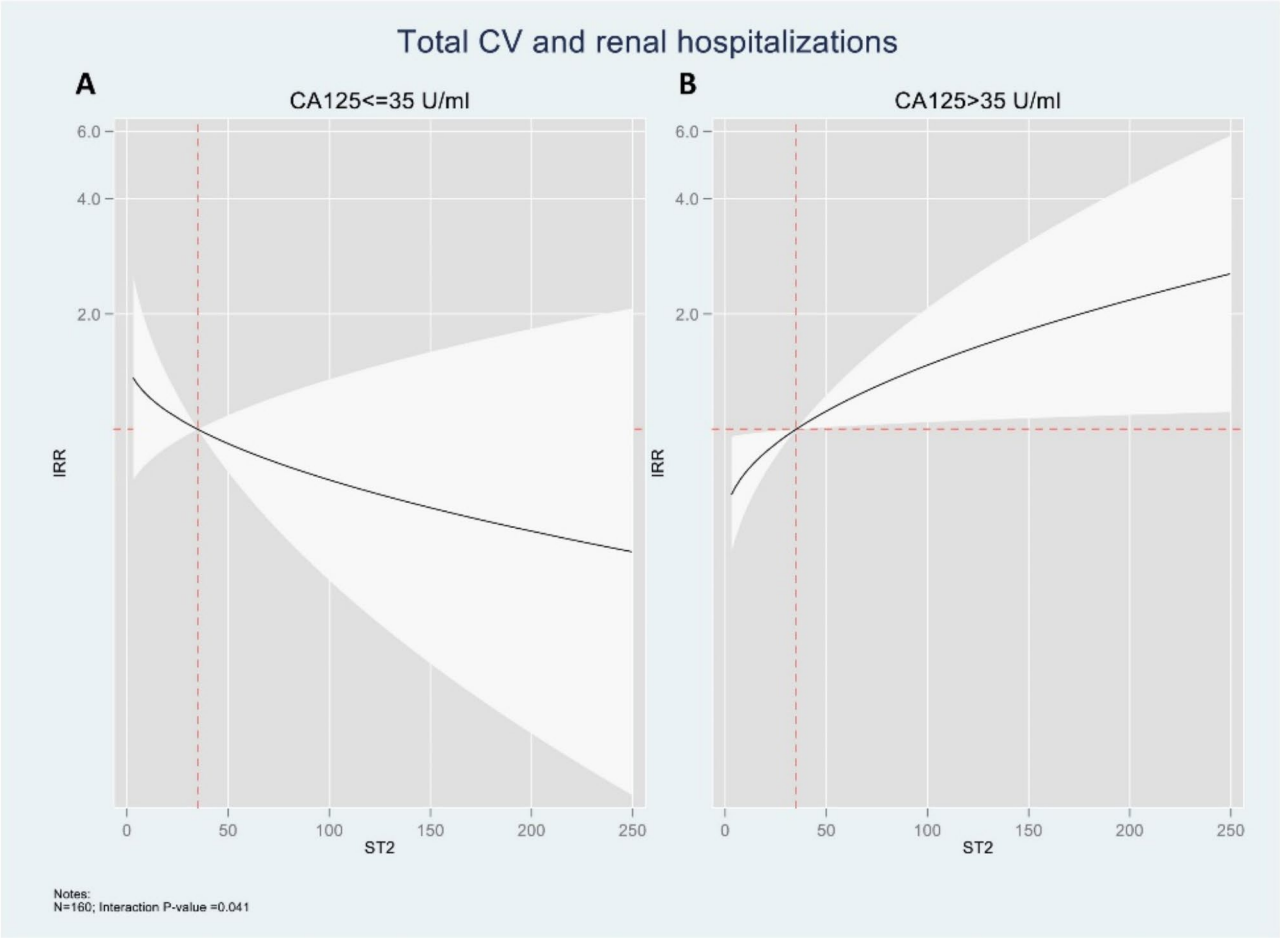

Fig. 1. sST2 and its association with the risk of total CV-renal rehospitalization expressed as incidence rate ratios. sST2 was modelled linearly with the gradient of risk. The associations between sST2 (along the continuum) and CV-renal rehospitalizations were significantly modulated by CA125 status (interaction $p = 0.041$). (**A**) sST2 was not related to the endpoint when CA125 ≤ 35 U/ml ($p = 0.324$). (**B**) sST2 was positive and significantly associated with an increased risk of CV-renal hospitalizations in patients with CA125 > 35 U/ml ($p = 0.027$).

Conclusion

The present sub-study of the IMPROVE-HF trial, performed in patients with AHF and renal dysfunction on admission, shows that sST2 mainly predicts cardiovascular-renal rehospitalizations when CA125 is elevated (> 35 U/ml). Larger translational studies are warranted to confirm the current findings and unravel the mechanisms behind them.

Fig. 2. sST2 and its association with total HF-hospitalizations expressed as incidence rate ratios. sST2 was modelled linearly with the gradient of risk. The associations between sST2 (along the continuum) and Total HF-rehospitalizations were not modulated by CA125 status (interaction $p = 0.127$).

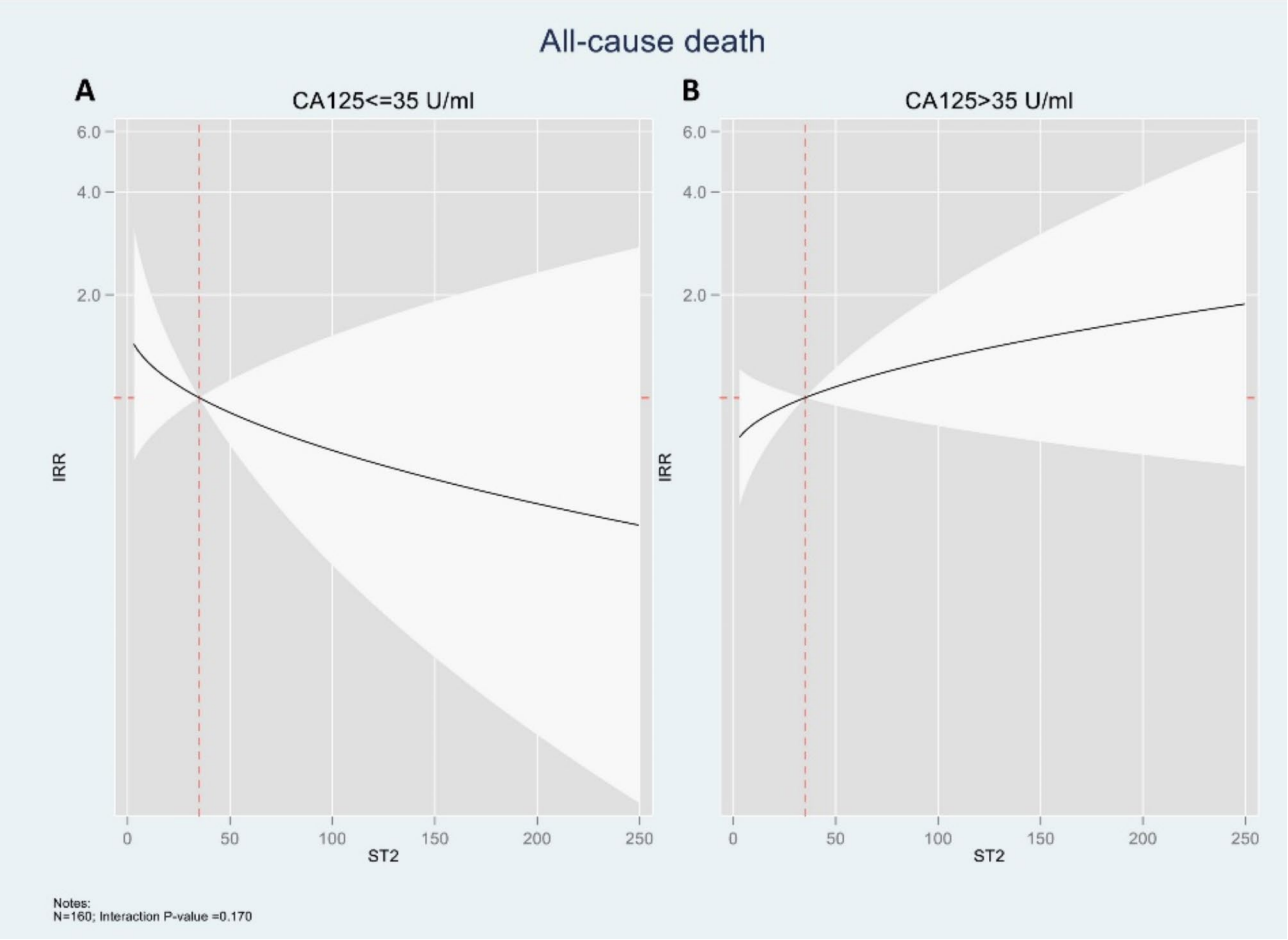

Fig. 3. sST2 and its association with all cause of death expressed as incidence rate ratios. sST2 was modelled linearly with the gradient of risk. sST2 was not associated with all-cause of death according to CA125 levels (p-value for interaction = 0.170).

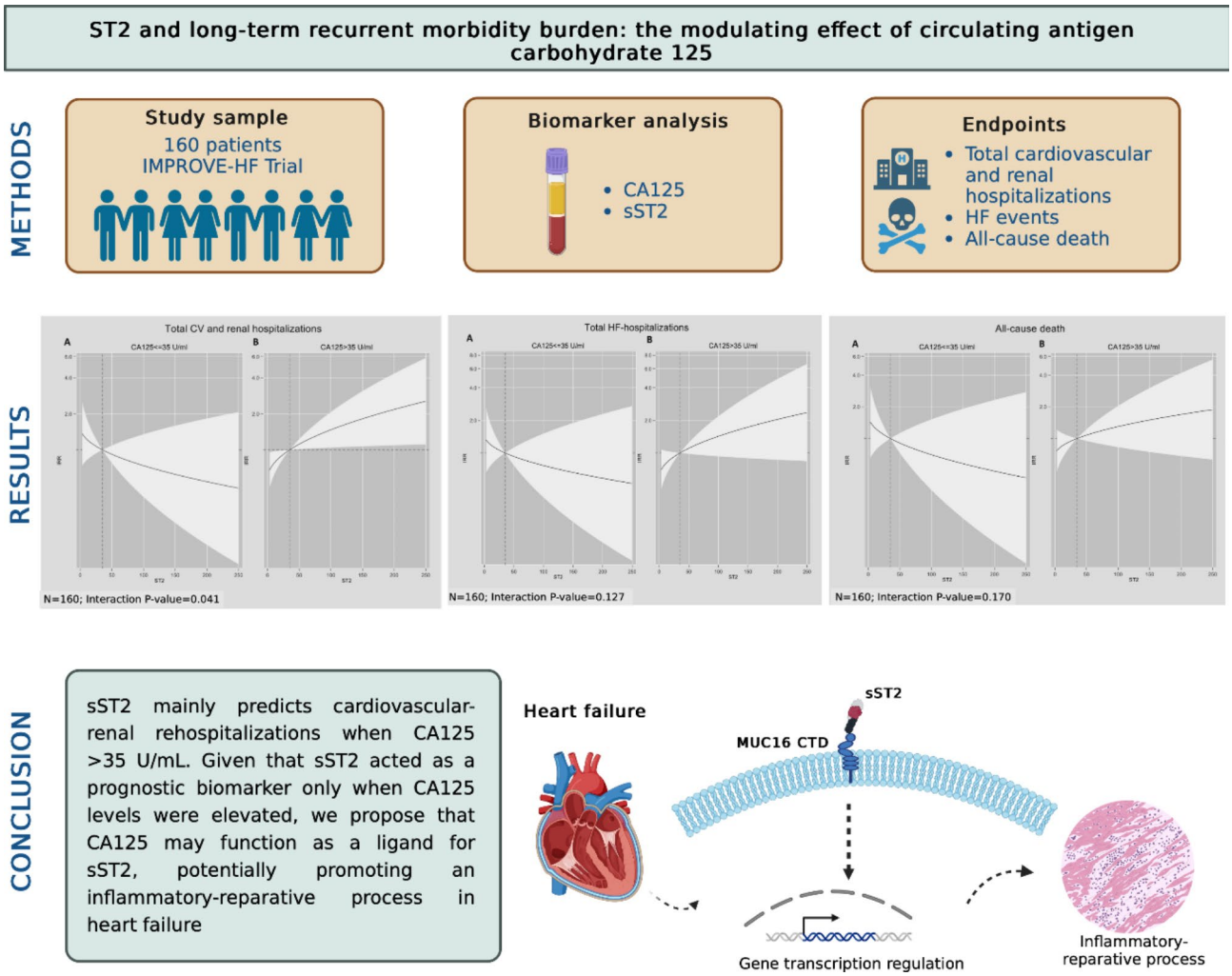

Fig. 4. Graphical abstract.

Data availability

The datasets used and/or analysed during the current study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request. Data are located in controlled access data storage at Hospital Clínico Universitario de Valencia.

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Author contributions

ERL analyses sST2 levels, wrote the main manuscript text and prepared Fig. 4.RE wrote the main manuscript text and revised Fig. 4GM participated on acquisition data ES participated on acquisition and data analysis SV participated on acquisition data JS contributed on the conception and study designAB contributed on the conception and study designJN contributed con the conception, study design, data analysis and prepared Figs. 1 and 2, and supplemental filesAll authors reviewed the manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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Correspondence and requests for materials should be addressed to J.N.