JACC: HEART FAILURE
VOL. 5, NO. 4, 2017

ISSN 2213-1779/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jchf.2016.12.016

Meta-Analysis of Soluble Suppression of Tumorigenicity-2 and Prognosis in Acute Heart Failure

Alberto Aimo, MD,[a] Giuseppe Vergaro, MD,[a,b] Andrea Ripoli, EngD,[b] Antoni Bayes-Genis, MD, PhD,[c] Domingo A. Pascual Figal, MD, PhD,[d] Rudolf A. de Boer, MD,[e] Johan Lassus, MD, PhD,[f] Alexandre Mebazaa, MD, PhD,[g] Etienne Gayat, MD, PhD,[g] Tobias Breidthardt, MD,[h] Zaid Sabti, MD,[h] Christian Mueller, MD,[h] Hans-Peter Brunner-La Rocca, MD,[i] W.H. Wilson Tang, MD,[j] Justin L. Grodin, MPH,[k] Yuhui Zhang, MD,[l] Paulo Bettencourt, MD,[m] Alan S. Maisel, MD,[n] Claudio Passino, MD,[a,b] James L. Januzzi, MD,[o] Michele Emdin, MD, PhD[a,b]

ABSTRACT

OBJECTIVES The aim of this study was to perform a meta-analysis of currently available data regarding the prognostic significance of soluble suppression of tumorigenecity-2 (sST2) concentration in acute heart failure (AHF).

BACKGROUND Concentration of sST2 may have prognostic value in AHF. A comprehensive assessment of all available studies regarding sST2 in AHF is lacking.

METHODS Three databases (MEDLINE, Cochrane Library, and Scopus) were searched. Inclusion criteria were follow-up studies, papers published in English, enrollment of patients with AHF, and availability of median hazard ratios for all-cause death and other outcome measures, when available.

RESULTS Ten studies were included, with a global population of 4,835 patients and a median follow-up duration of 13.5 months. The following global hazard ratios calculated for $\log_2$(sST2) were admission sST2 and all-cause death, 2.46 (95% confidence interval [CI]: 1.80 to 3.37; $p < 0.001$); discharge sST2 and all-cause death, 2.06 (95% CI: 1.37 to 3.11; $p < 0.001$); admission sST2 and cardiovascular death, 2.29 (95% CI: 1.41 to 3.73; $p < 0.001$); discharge sST2 and cardiovascular death, 2.20 (95% CI: 1.48 to 3.25; $p < 0.001$); admission sST2 and heart failure (HF) hospitalization, 1.21 (95% CI: 0.96 to 1.52; $p = 0.060$); discharge sST2 and HF hospitalization, 1.54 (95% CI: 1.03 to 2.32; $p = 0.007$); admission sST2 and all-cause death or HF hospitalization, 1.74 (95% CI: 1.24 to 2.45; $p < 0.001$); and discharge sST2 and all-cause death or HF hospitalization, 1.63 (95% CI: 1.14 to 2.33; $p < 0.001$).

CONCLUSIONS Plasma sST2 has prognostic value with respect to all-cause and cardiovascular death as well as the composite outcome of all-cause death or HF hospitalization, with both admission and discharge values having prognostic efficacy. Discharge sST2, but not admission sST2, is predictive of HF rehospitalization during follow-up. (J Am Coll Cardiol HF 2017;5:287–96) © 2017 by the American College of Cardiology Foundation.

From [a]Scuola Superiore Sant'Anna, Pisa, Italy; [b]Fondazione Toscana G. Monasterio, Pisa, Italy; [c]Hospital Universitari Germans Trias i Pujol, Barcelona, Spain; [d]Hospital Universitario Arrixaca, University of Murcia, Murcia, Spain; [e]University Medical Center Groningen, Groningen, the Netherlands; [f]Heart and Lung Center, Helsinki University Hospital and Helsinki University, Helsinki, Finland; [g]INSERM U 942, Université Paris Diderot, APHP Hôpitaux Universitaires Saint Louis Lariboisière, Paris, France; [h]Universitätsspital Basel, Basel, Switzerland; [i]Department of Cardiology, Maastricht University Medical Centre, Maastricht, the Netherlands; [j]Heart and Vascular Institute, Cleveland Clinic, Cleveland, Ohio; [k]Department of Internal Medicine, Division of Cardiology, University of Texas Southwestern Medical Center, Dallas, Texas; [l]Peking Union Medical College, Beijing, China; [m]University of Porto Medical School, Porto, Portugal; [n]University of California, San Diego, School of Medicine, San Diego, California; and the [o]Massachusetts General Hospital and Harvard Clinical Research Institute, Boston, Massachusetts. Dr. Bayes-Genis has received lecture honoraria from Critical Diagnostics. Dr. Januzzi has received grant support from Siemens, Singulex, and Prevencio; has received consulting income from Roche Diagnostics, Critical Diagnostics, Sphingotec, Phillips, and Novartis; and

ABBREVIATIONS AND ACRONYMS

AHF = acute heart failure

CHF = chronic heart failure

CI = confidence interval

CV = cardiovascular

HF = heart failure

HR = hazard ratio

sST2 = soluble suppression of tumorigenecity-2

ST2 = suppression of tumorigenecity-2

Soluble suppression of tumorigenecity-2 (sST2) is the circulating form of the receptor for interleukin-33. A membrane-bound form of the suppression of tumorigenecity-2 (ST2) receptor is known as ST2 ligand. The interaction between interleukin-33 and ST2 ligand exerts anti-inflammatory and antifibrotic effects in the damaged heart; these effects are blunted by sST2, which acts as a decoy receptor for interleukin-33 (1). In 2003, increased sST2 concentrations were first reported in patients with chronic heart failure (CHF) (2). Since then, sST2 has been extensively studied in both acute heart failure (AHF) and CHF, demonstrating substantial potential as a prognostic biomarker in both settings (3–5). Additionally, sST2 appears somewhat unencumbered by many of the issues limiting B-type natriuretic peptide or its amino-terminal equivalent: unlike natriuretic peptides, sST2 has a narrow range of biological variation, and plasma concentrations of sST2 are less significantly influenced by age, sex, body mass index, and comorbidities (6).

Given potential advantages of sST2 as a biomarker of prognosis in patients with AHF, an international consensus panel on sST2 recognized the independent prognostic value of sST2 with respect to the short-, intermediate-, and long-term risk for major adverse cardiovascular (CV) events, recommending the measurement of plasma sST2 both at admission, for initial risk assessment and triage, and at discharge, to inform post-treatment decision making (4). In contrast, the American College of Cardiology Foundation and American Heart Association adopted a more prudent approach in their guidelines, supporting sST2 measurement as an additive tool for risk stratification in patients with AHF (Class IIb, Level of Evidence: A); no indications are provided for the modality of sampling (single or repeated) (7). No specific recommendations on sST2 in AHF have been provided by the most recent European Society of Cardiology guidelines (8).

Because of discordant conclusions creating ambiguity, we believed it worthwhile to carefully examine and meta-analyze evidence supporting the measurement of sST2, to assess the prognostic role of this biomarker in patients with heart failure (HF). Following the first meta-analysis on sST2 confirming its prognostic value in patients with stable CHF (9), we have now performed a similar meta-analysis on sST2 and prognosis in patients with AHF.

METHODS

DATA SOURCES, SEARCH STRATEGY, AND ELIGIBILITY CRITERIA. The meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (10). In May 2016, 2 reviewers (A.A. and G.V.) independently searched 3 databases (MEDLINE, Cochrane Library, and Scopus). The search terms, deliberately generic, were "ST2" OR "sST2" AND "heart failure" OR "cardiac failure" OR "cardiac dysfunction" OR "cardiac insufficiency" OR "left ventricular dysfunction."

The inclusion criteria were as follows: 1) follow-up studies, including post hoc analyses of randomized clinical trials; 2) papers in English; 3) enrollment of patients with AHF (either de novo AHF or worsening CHF requiring hospitalization); and 4) availability, either from published papers or from the investigators, of median hazard ratios (HRs) for all-cause death and possibly other outcome measures (CV death, HF hospitalization, all-cause death, and HF hospitalization) on univariate analysis.

The exclusion criteria were as follows: 1) sST2 not considered independently but only as an element of a prognostic score; and 2) studies of patients with end-stage HF or with acute coronary syndromes.

When a study could not be included only because of a lack of crude data on HRs and 95% confidence intervals (CIs), a request was made to the corresponding investigator of the study to provide the data.

The following data were extracted from each study: first investigator's last name, publication year, country where the study was conducted, study period, number of patients enrolled, follow-up duration, outcomes evaluated, and all demographic and clinical baseline data provided. The outcomes to be considered in the comprehensive analysis were decided after selecting the studies according to the aforementioned criteria. The data were extracted by a reviewer (A.A.) and checked for accuracy by a second reviewer (G.V.).

participates in clinical endpoint committees for Novartis, Amgen, Janssen, and Boehringer Ingelheim. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. John R. Teerlink, MD, served as Guest Editor for this paper.

Manuscript received September 21, 2016; revised manuscript received October 31, 2016, accepted December 29, 2016.

STATISTICAL ANALYSIS. Statistical analysis was performed using R version 3.2.3, metafor package (11).

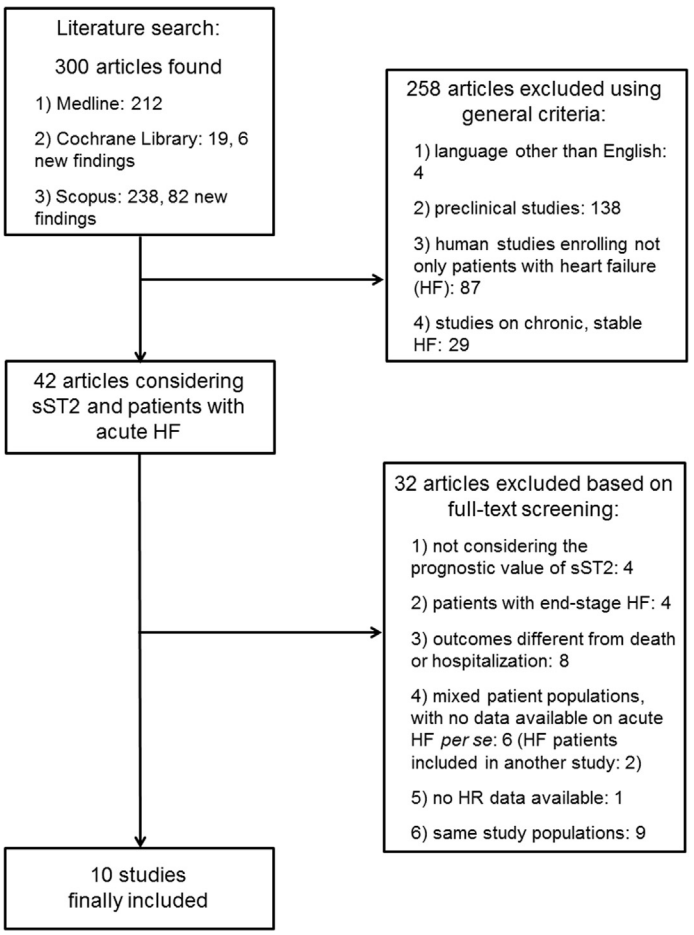
The HRs for all-cause and CV death with the corresponding 95% CIs were recorded; in all cases, the HRs were calculated for $\log_2$(sST2), so that the reported HRs represented the risk per doubling of sST2 (12). Because of the small study number, and the consequent skewed distribution of HRs, $\log_{10}$ transformation of HRs was performed (11). The summary of effect size was estimated by using both the fixed-effects model and the random-effects model. These models rely on different assumptions (fixed-effects model: same mean effect size, zero between-study variance; random-effects model: different mean effect size, between-study variance), and the use of both has been recommended (11).

The summary of effect size enabled the calculation of global log(HR) with its 95% CI. The z statistic was used to evaluate the null hypothesis (that sST2 value is not predictive of outcome). The corresponding p value was calculated; a p value < 0.05 was considered to indicate statistical significance.

The heterogeneity analysis was compatible only with the random-effects model. Because of the small number of studies, the Cochran Q test was not used (13). The following measures were calculated: τ^2 (the estimated amount of total heterogeneity), τ (the square root of τ^2), I^2 (total heterogeneity/total variability), H^2 (total variability/sampling variability), and H (the square root of H^2); the 95% CI was calculated for all these measures.

Meta-regression analysis was performed to search for population characteristics unevenly distributed among studies, thus potentially contributing to the different estimations of the predictive value of sST2. Finally, funnel-plot analysis allowed us to verify the presence of a "file-drawer problem" (i.e., the lack of publication of studies with negative results). The "trim-and-fill" method was used to estimate the number of supposedly unpublished studies (11).

FIGURE 1 Flowchart of Study Selection



HF = heart failure; HR = hazard ratio; sST2 = soluble suppression of tumorigenecity-2.

RESULTS

SEARCH AND STUDY SELECTION. The search process is summarized in **Figure 1**. Ten studies were finally included (14–23), with a final population of 4,835 patients. The main patients' characteristics are summarized in **Table 1**. The HRs relative to sST2 values either at admission or at discharge during the index hospitalization were considered. **Table 2** shows the HRs for the different outcomes of all-cause death, CV death, HF hospitalization, and all-cause death or HF hospitalization. All HRs given in the following paragraph were calculated using the random-effects model; the corresponding results obtained using the fixed-effects model are reported in Online Table 1.

SUMMARY OF EFFECT SIZE. Admission sST2 and all-cause death. The global log(HR) was 0.39 (95% CI: 0.25 to 0.53) (**Figure 2A**), and the global HR was 2.46 (95% CI: 1.80 to 3.37). The z value was 5.63 ($p < 0.001$). When excluding the study by Zhang et al. (23), for which only cumulative data on all-cause death and heart transplantation were available, the HR was nearly unchanged at 2.42 (95% CI: 1.65 to 3.56) ($p < 0.001$).

Discharge sST2 and all-cause death. The global log(HR) was 0.31 (95% CI: 0.14 to 0.49) (**Figure 2B**), and the global HR was 2.06 (95% CI: 1.37 to 3.11). The z value was 3.45 ($p < 0.001$). When excluding the

TABLE 1 Main Features of Study Populations

First Author (Year) (Ref. #)	Original Study Publication Year	Patients, n	Age, Mean/ Median, yrs	Men, %	Assay	Worsening CHF vs. De Novo AHF, %	LVEF, Mean/ Median, %	CAD, %
Breidthardt (2013) (14)	2013	207	80	57	Presage	50-50	40	48
Frioes (2015) (15)	2015	195	75	49	R&D	88-12	NA	43
Gandhi (2014) (16)	2014	39	72	74	Presage	80-20	*57*	65
Lassus (2013) (17)	2013	728	69	65	Presage	55-45	*45*	49
Llibre (2016) (18)	2016	182	76	54	Presage	64-36	42	35
Maisel (2014) (19)	2008	534	71	61	Presage	NA	33	66
Pascual-Figal (2011) (20)	2011	107	72	56	Presage	59-41	47	34
Sanders-van Wijk (2015) (21)	2009	457	77	61	Presage	NA	35	53
Tang (2016) (22)	2011	858	66	68	Presage	NA	26	60
Zhang (2014) (23)	2014	1,528	58	70	Presage	77-23	40	47

TABLE 1 Continued

First Author (Year) (Ref. #)	SBP, Mean/ Median, mm Hg	Basal Heart Rate, Mean/Median, beats/min	Basal Creatinine, Mean/Median, mg/dl	Follow-Up Duration, days	All-Cause Deaths, n (% of Entire Population)	CV Deaths, n (% of All-Cause Deaths)	HF Hospitalization, n	All-Cause Death or HF Hospitalization, n
Breidthardt (2013) (14)	137	*86*	1.2	368	69 (33.3)	51 (73.9)	41	99
Frioes (2015) (15)	*130*	NA	NA	180	29 (14.9)	22 (75.9)	50	66
Gandhi (2014) (16)	144	*82*	*1.2*	365	11 (28.2)	8 (72.7)	17	23
Lassus (2013) (17)	140	84	*1.0*	365	200 (27.5)	NA	NA	NA
Llibre (2016) (18)	NA	NA	*1.2*	365	23 (12.6)	22 (95.7)	23	41
Maisel (2014) (19)	119	74	1.3	545	160 (30.0)	NA	148	240
Pascual-Figal (2011) (20)	150	101	1.2	739	29 (27.1)	17 (58.9)	43	60
Sanders-van Wijk (2015) (21)	122	76	1.2	540	186 (40.7)	137 (73.7)	153	243
Tang (2016) (22)	127	80	1.4	30/180	97 (11.3)	NA	NA	99
Zhang (2014) (23)	119	78	1.0	573	300 (19.6)	NA	NA	NA

Characteristics from analyzed studies are provided. All studies used the Presage assay except for Frioes et al. (15), who used the R&D Systems assay. The sources of significant heterogeneity in the assessment of the predictive value of sST2 (prevalence of hypertension and HF drugs) are reported; LVEF, SBP, and creatinine values are reported as either mean or median (in *italics*), according to the way in which these data were reported in the studies. The number of all-cause deaths, CV deaths, hospitalizations for HF, and all-cause deaths or HF hospitalizations are also provided. In the study by Lassus et al. (17), among the 5,306 subjects included in the original study, only 728 had sST2 measured at admission; only this subgroup was considered for the present analysis. In the cohort of Sanders-van Wijk et al. (21), only patients with AHF were included. In the study by Maisel et al. (19), the hazard ratio was computed on a longer follow-up duration (median: 545 days) than in the original study (30 days). Finally, in the study by Tang et al. (22), different follow-up durations were considered for all-cause death (97 events over 180 days) and all-cause death or hospitalization (99 events over 30 days).

AHF = acute heart failure; CAD = coronary artery disease; CHF = chronic heart failure; CV = cardiovascular; HF = heart failure; LVEF = left ventricular ejection fraction; NA = data not available; SBP = systolic blood pressure; sST2 = soluble suppression of tumorigenicity-2.

study not using the Presage assay (15), the HR was 1.98 (95% CI: 1.19 to 3.29), which was still significant ($p < 0.001$).

Admission sST2 and CV death. The global log(HR) was 0.36 (95% CI: 0.15 to 0.57) (Figure 3A); the global HR was 2.29 (95% CI: 1.41 to 3.73). The z value was 3.45 ($p < 0.001$).

Discharge sST2 and CV death. The global log(HR) was 0.34 (95% CI: 0.17 to 0.51) (Figure 3B), and the global HR was 2.20 (95% CI: 1.48 to 3.25). The z value was 3.94 ($p < 0.001$). When excluding the study not using the Presage assay (15), the HR remained robust at 1.98 (95% CI: 1.19 to 3.29) ($p < 0.001$).

Admission sST2 and HF hospitalization. The global log(HR) was 0.08 (95% CI: −0.02 to 0.18) (Figure 4A); the global HR was 1.21 (95% CI: 0.96 to 1.52). The z value was 1.59, and the null hypothesis was retained ($p = 0.060$).

Discharge sST2 and HF hospitalization. The global log(HR) was 0.19 (95% CI: 0.01 to 0.37) (Figure 4B); the global HR was 1.54 (95% CI: 1.03 to 2.32). The z value was 2.09 ($p = 0.007$). When excluding the study not using the Presage assay (15), the HR was 1.66 (95% CI: 0.82 to 3.39) ($p = 0.085$).

Admission sST2 and all-cause death or HF hospitalization. The global log(HR) was 0.24 (95% CI: 0.09 to 0.39) (Figure 5A); the global HR was 1.74 (95% CI: 1.24 to 2.45). The z value was 3.19 ($p < 0.001$).

Discharge sST2 and all-cause death or HF hospitalization. The global log(HR) was 0.21 (95% CI: 0.06 to 0.37) (Figure 5B); the global HR was 1.63 (95% CI: 1.14 to 2.33). The z value was 2.68 ($p < 0.001$). When excluding the study not using the Presage assay (15), the HR decreased to 1.69 (95% CI: 0.95 to 2.99) ($p = 0.070$).

TABLE 2 Prognostic Role of Soluble Suppression of Tumorigenecity-2 in Acute Heart Failure

	sST2		All-Cause Death	
First Author (Year) (Ref. #)	Admission	Discharge	Admission sST2	Discharge sST2
Breidthardt (2013) (14)	78.0 (46.0–121.0)	NA	3.71 (2.31–5.94)	3.84 (2.08–7.06)
Frioes (2015) (15)	NA	NA	NA	2.58 (1.69–3.93)
Gandhi (2014) (16)	97.0 (75.0–142.0)	NA	4.23 (1.05–19.5)	NA
Lassus (2013) (17)	75.3 (43.9–121.2)	NA	4.16 (2.84–6.08)	NA
Llibre (2016) (18)	59.0 (IR NA)	36.6 (IR NA)	1.58 (1.12–2.24)	2.94 (1.27–6.76)
Maisel (2014) (19)	NA	NA	NA	1.29 (1.10–1.50)
Pascual-Figal (2011) (20)	63.0 (40.3–106.3)	NA	2.00 (1.37–2.91)	NA
Sanders-van Wijk (2015) (21)	NA	36.1 (26.2–52.7)	NA	1.51 (1.31–1.76)
Tang (2016) (22)	NA	NA	1.62 (1.31–2.01)	NA
Zhang (2014) (23)	37.1 (25.2–55.7)	NA	*2.73 (2.42–3.07)*	NA

TABLE 2 Continued

	CV Death		HF Hospitalization		All-Cause Death/HF Hospitalization	
First Author (Year) (Ref. #)	Admission sST2	Discharge sST2	Admission sST2	Discharge sST2	Admission sST2	Discharge sST2
Breidthardt (2013) (14)	3.73 (2.18–6.36)	NA	1.55 (0.85–2.82)	NA	2.56 (1.74–3.74)	NA
Frioes (2015) (15)	NA	3.14 (1.89–5.22)	NA	1.53 (1.14–2.05)	NA	1.69 (1.31–2.18)
Gandhi (2014) (16)	3.96 (0.91–12.6)	NA	NA	NA	4.36 (1.80–10.50)	NA
Lassus (2013) (17)	NA	NA	NA	NA	NA	NA
Llibre (2016) (18)	1.48 (1.01–2.18)	3.66 (1.51–8.89)	1.34 (0.91–1.97)	4.08 (1.79–9.32)	1.44 (1.08–1.91)	3.47 (1.82–6.64)
Maisel (2014) (19)	NA	NA	NA	NA	NA	1.16 (1.02–1.31)
Pascual-Figal (2011) (20)	1.94 (1.19–3.17)	1.94 (1.19–3.17)	1.04 (0.76–1.43)	1.04 (0.76–1.43)	1.31 (1.01–1.70)	NA
Sanders-van Wijk (2015) (21)	NA	1.57 (1.32–1.87)	NA	1.41 (1.17–1.71)	NA	1.48 (1.27–1.72)
Tang (2016) (22)	NA	NA	NA	NA	1.37 (1.10–1.71)	NA
Zhang (2014) (23)	NA	NA	NA	NA	NA	NA

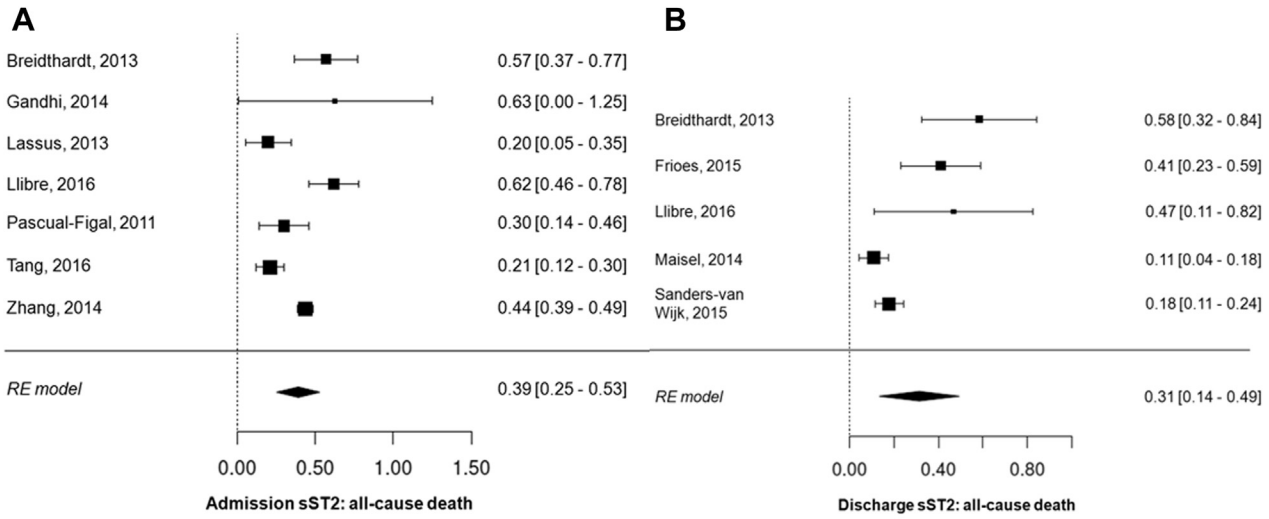
Values are hazard ratio (95% confidence interval). In the study by Zhang et al. (23), the HR was calculated for all-cause death and heart transplantation.
Abbreviations as in Table 1.

META-REGRESSION ANALYSIS AND ASSESSMENT OF PUBLICATION BIAS. These analyses were performed for the endpoint of all-cause death with respect to sST2 concentration at either admission or discharge. Of the available data, 7 and 5 studies, respectively, reported HRs for these endpoints, whereas 4 or 3 studies provided HRs for all other outcome measures (for details, see **Table 2**).

Admission sST2 and all-cause death. The following measures of heterogeneity were calculated with the random-effects model: tau^2 = mean 0.03 (95% CI 0.01 to 0.15); tau = 0.16 (0.08-0.39); I^2 = 86.54% (60.89% to 97.50%); H^2 = 7.43 (2.56 to 40.05); H 2.73 (1.60 to 6.33). The values of H (significant heterogeneity when the CI lower limit is >1) and I^2 (86.54%; high heterogeneity when >75%) suggested significant heterogeneity among studies (11), which was confirmed by the dispersion of studies in the forest plot (**Figure 2A**). The discrepancy between the HRs calculated using the fixed-effects and random-effects models further confirmed the heterogeneity among studies; in turn, such heterogeneity justified the preferential consideration of HRs calculated using the random-effects model (24). On jackknife analysis, the study by Zhang et al. (23) was the main contributor to the global HR, and the exclusion of each study changed the overall HR. All population variables reported in at least 5 studies were considered as potential sources of heterogeneity: publication year of the original study, age, gender, left ventricular ejection fraction, type of acute HF (i.e., *de novo* HF or worsening chronic HF), systolic blood pressure, basal heart rate, coronary artery disease, basal creatinine, hemoglobin, hypertension, diabetes, NT-proBNP and sST2 at admission, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers or diuretics at admission, follow-up duration (days). Only baseline creatinine emerged as a significant source of heterogeneity. Finally, funnel-plot analysis (fixed-effects model) did not show evidence of a publication bias (Online Figure 1A).

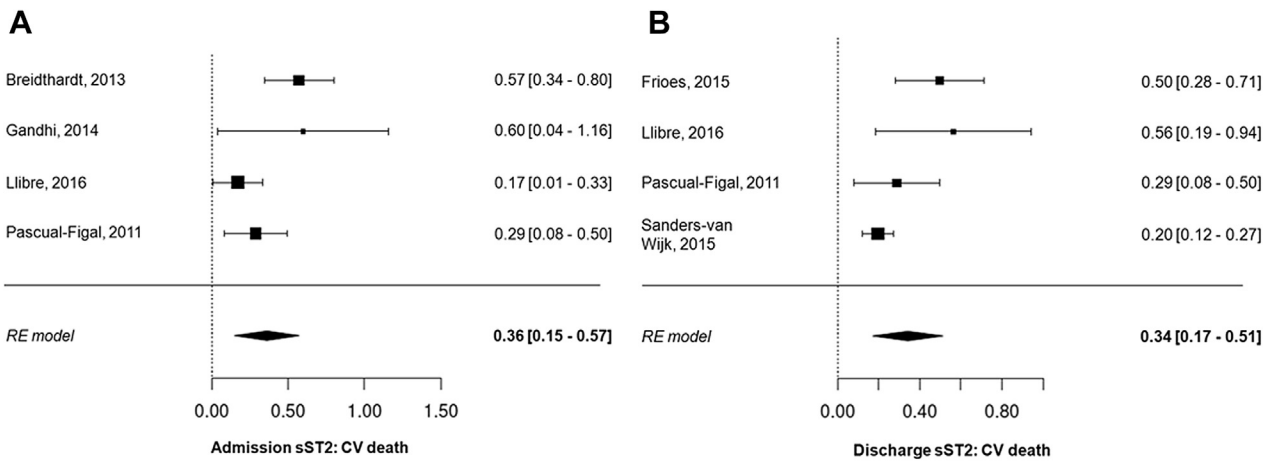
Discharge sST2 and all-cause death. Significant heterogeneity among studies was detected, as visually represented in **Figure 2B**. The study by Llibre et al. (18) was the main contributor to the global HR, and the exclusion of each study changed the estimate of the predictive value of sST2. Population characteristics

FIGURE 2 Risk for All-Cause Death



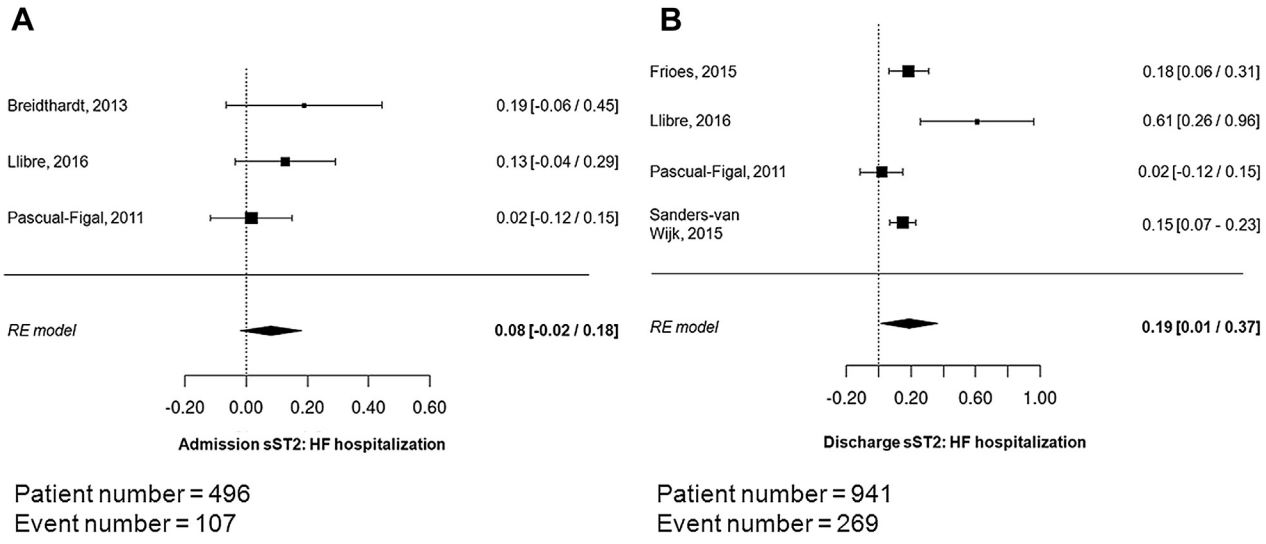
Admission **(A)** and discharge soluble suppression of tumorigenicity-2 **(B)** Forest-plot analysis. Hazard ratios and the corresponding 95% confidence intervals are reported. Log_{10} values are provided (0 = no prognostic value). RE = random-effects; sST2 = soluble suppression of tumorigenicity-2.

FIGURE 3 Risk for Cardiovascular Death



Admission **(A)** and discharge soluble suppression of tumorigenicity-2 **(B)** Forest-plot analysis. Hazard ratios and the corresponding 95% confidence intervals are reported. Log_{10} values are provided (0 = no prognostic value). CV = cardiovascular; other abbreviations as in Figures 1 and 2.

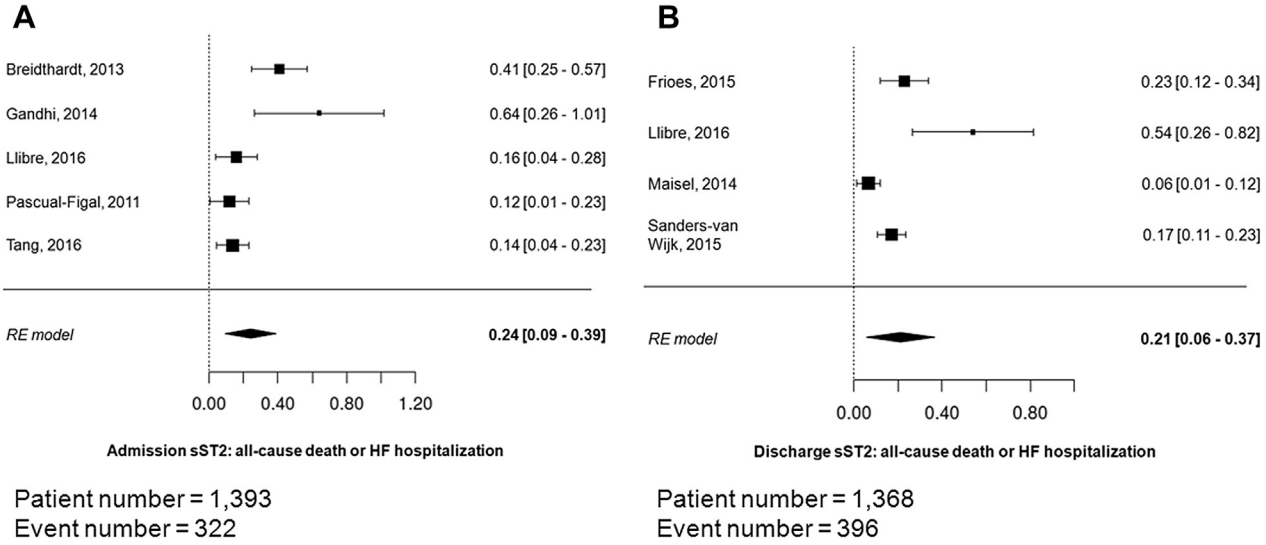
FIGURE 4 Risk for Heart Failure Hospitalization



Admission **(A)** and discharge soluble suppression of Tumorigenicity-2 **(B)**. Forest-plot analysis. Hazard ratios and the corresponding 95% confidence intervals are reported. Log_{10} values are provided (0 = no prognostic value). Abbreviations as in Figures 1 and 2.

reported in at least 4 studies were considered. The following variables emerged as significant sources of heterogeneity: publication year of the original study, left ventricular ejection fraction, systolic blood pressure, basal heart rate, coronary artery disease, and follow-up duration. Funnel-plot analysis suggested a publication bias, with 2 apparently missing studies on the left side ($p < 0.001$) (Online Figure 1B).

FIGURE 5 Risk for All-Cause Death or Heart Failure Hospitalization



Admission **(A)** and discharge soluble suppression of Tumorigenicity-2 **(B)**. Forest-plot analysis. Hazard ratios and the corresponding 95% confidence intervals are reported. Log_{10} values are provided (0 = no prognostic value). Abbreviations as in Figures 1 and 2.

DISCUSSION

In the present meta-analysis of 10 studies of the predictive value of sST2 in patients with AHF (assessing a total of 4,835 patients over a median 13.5-month follow-up period), concentration of sST2 assayed either at admission or at discharge was predictive of all-cause death, CV death, and the composite outcome of all-cause death or HF hospitalization. Additionally, discharge sST2 concentration was predictive of HF hospitalization during follow-up. Our findings lend robust meta-analytic support to the value of sST2 as a prognostic biomarker in patients with AHF. Notably, although admission values were prognostic, the finding that discharge sST2 concentration predicts HF hospitalization is important, as few other biomarkers achieve this goal (25,26).

In vitro studies have identified stretch-induced secretion of sST2 from cardiac myofibroblasts (2,27,28); this mechanism, which mirrors that of natriuretic peptide production and secretion, could be elicited by fluid overload and increase in ventricular pressures, which are typical of the presenting phase of AHF. As mentioned, sST2 acts as a decoy receptor for interleukin-33, whose binding with ST2 ligand exerts anti-inflammatory and antifibrotic effects in the damaged heart (1,4). Elevation of sST2 concentrations likely reflects activation of this pathway, but sST2 release has also other recognized triggers, such as local or systemic inflammation (disease settings in which sST2 has an established predictive value for all-cause mortality) (29,30).

In a previous meta-analysis, we demonstrated a prognostic role for sST2 in patients with stable CHF with regard to all-cause death (median HR: 1.76) and CV death (HR: 1.79) (9). The corresponding HRs for these outcomes are higher in the present analysis of AHF, when considering both admission and discharge values. Median sST2 levels at admission for AHF are markedly higher than in patients with CHF in stable condition, consistent with the theory that sST2 concentration reflects chronic CV damage during clinical stability, whereas in acute settings, sST2 indicates such damage plus acute CV stress. Our data should not imply that sST2 is more meaningful for prognostic value in patients with AHF, however, and great care should be taken when comparing the results of the present and the previous meta-analyses. For example, median follow-up duration was double in stable CHF than in AHF (27.0 months vs. 13.5 months), and the prognostic efficacy of biomarkers generally decreases over longer follow-up periods (25); furthermore, higher HRs in AHF than in stable CHF could simply reflect lower sample sizes in studies of AHF; HR estimates are often greater in smaller study populations (29).

STUDY LIMITATIONS. By design, our analysis does not allow us to demonstrate the superiority of sST2 compared with other proposed biomarkers of AHF, such as midregional proadrenomedullin, highly sensitive troponin, growth differentiation factor-15, or copeptin (25), nor did we examine the incremental prognostic value of sST2 over established risk factors. Furthermore, although we are providing the first meta-analysis of sST2 in AHF, more data are needed regarding the integrative clinical value of sST2 relative to natriuretic peptides or risk scores for the optimal care of patients with HF. A degree of heterogeneity among studies was found, but the various studies reported different population characteristics, thus hindering a thorough assessment of the sources of heterogeneity; small sample sizes of several studies represented another potential problem for this analysis (30). Furthermore, the studies considered different endpoints, and only 1 study (18) provided sST2 values at both admission and discharge. It would have been interesting to assess the absolute changes in sST2 during the index hospitalization. In a small study (which could not be included in the present analysis because of a lack of HR values), percentage change in sST2 from admission to discharge was predictive of 90-day mortality; patients whose sST2 values decreased by 15.5% or more during the study period had a 7% chance of death, whereas those whose sST2 levels failed to decrease by 15.5% in this time interval had a 33% chance of dying (31). Similar findings were reported by Breidthardt et al. (14), who found that the percentage change of sST2 over the first 48 hours significantly predicted long-term mortality in univariate analysis and after adjustment for several clinical risk factors. Finally, by study design, we did not include studies considering mixed population (all [32-36] but 1 [37] enrolling patients with acute dyspnea), but patients with HF from 2 studies (35,36) were included because they had sST2 determined with the Presage assay and had been included in the study by Lassus et al. (17).

CONCLUSIONS

The present meta-analysis provides a demonstration of sST2 efficacy in the prediction of clinically meaningful outcomes in patients with AHF. These findings support current American College of Cardiology

Foundation and American Heart Association recommendation on sST2 assay for risk stratification of patients with AHF (7). Further studies should establish the optimal timing of sST2 sampling and, most important, assess whether specific action in response to the prognostic information conveyed by sST2 indeed improves patient status and outcomes.

ADDRESS FOR CORRESPONDENCE: Dr. Alberto Aimo, Scuola Superiore Sant'Anna, Piazza Martiri della Libertà, 33, 56127 Pisa, Italy. E-mail: albertoaimo@libero.it.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The present meta-analysis demonstrates that sST2 assay aids in the risk stratification in patients with AHF, thus possibly assisting clinicians in therapeutic decision making.

TRANSLATIONAL OUTLOOK: By its nature, this work has no clear "bench-to-bedside" applications. Of note, several aspects of sST2 biology remain incompletely understood, thus providing interesting perspectives for translational research.

REFERENCES

1. Kakkar R, Lee RT. The IL-33/ST2 pathway: therapeutic target and novel biomarker. Nat Rev Drug Discov 2008;7:827–40.

2. Weinberg EO, Shimpo M, Hurwitz S, et al. Identification of serum soluble ST2 receptor as a novel heart failure biomarker. Circulation 2003;107:721–6.

3. Dieplinger B, Mueller T. Soluble ST2 in heart failure. Clin Chim Acta 2015;443:57–70.

4. Januzzi JL, Mebazaa A, Di Somma S. ST2 and prognosis in acutely decompensated heart failure: the International ST2 Consensus Panel. Am J Cardiol 2015;115 Suppl:26B–31B.

5. Januzzi JL, Pascual-Figal D, Daniels LB. ST2 testing for chronic heart failure therapy monitoring: the International ST2 Consensus Panel. Am J Cardiol 2015;115 Suppl:70B–5B.

6. Anand IS, Kempf T, Rector TS, et al. Serial measurement of growth-differentiation factor-15 in heart failure: relation to disease severity and prognosis in the Valsartan Heart Failure Trial. Circulation 2010;122:1387–95.

7. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62:e147–239.

8. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129–200.

9. Aimo A, Vergaro G, Passino C, et al. Prognostic value of soluble suppression of tumorigenicity-2 (sST2) in chronic heart failure: a meta-analysis. J Am Coll Cardiol HF 2017;5:280–6.

10. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.

11. Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Softw 2010;36:1–48.

12. Felker GM, Fiuzat M, Thompson V, et al. Soluble ST2 in ambulatory patients with heart failure: association with functional capacity and long-term outcomes. Circ Heart Fail 2013;6:1172–9.

13. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.

14. Breidthardt T, Balmelli C, Twerenbold R, et al. Heart failure therapy-induced early ST2 changes may offer long-term therapy guidance. J Card Fail 2013;19:821–8.

15. Frioes F, Lourenco P, Laszczynska O, et al. Prognostic value of sST2 added to BNP in acute heart failure with preserved or reduced ejection fraction. Clin Res Cardiol 2015;104:491–9.

16. Gandhi PU, Gaggin HK, Belcher AM, et al. Analysis of BAG3 plasma concentrations in patients with acutely decompensated heart failure. Clin Chim Acta 2015;445:73–8.

17. Lassus J, Gayat E, Mueller C, et al. Incremental value of biomarkers to clinical variables for mortality prediction in acutely decompensated heart failure: the Multinational Observational Cohort on Acute Heart Failure (MOCA) study. Int J Cardiol 2013;168:2186–94.

18. Llibre C, Zamora E, Caballero A, et al. The real-life value of ST2 monitoring during heart failure decompensation: impact on long-term readmission and mortality. Biomarkers 2016;21:225–32.

19. Maisel A, Xue Y, van Veldhuisen DJ, et al. Effect of spironolactone on 30-day death and heart failure rehospitalization (from the COACH study). Am J Cardiol 2014;114:737–42.

20. Pascual-Figal DA, Manzano-Fernandez S, Boronat M, et al. Soluble ST2, high-sensitivity troponin T- and N-terminal pro-B-type natriuretic peptide: complementary role for risk stratification in acutely decompensated heart failure. Eur J Heart Fail 2011;13:718–25.

21. Sanders-van Wijk S, van Empel V, Davarzani N, et al. Circulating biomarkers of distinct pathophysiological pathways in heart failure with preserved vs. reduced left ventricular ejection fraction. Eur J Heart Fail 2015;17:1006–14.

22. Tang WH, Wu Y, Grodin JL, et al. Prognostic value of baseline and changes in circulating soluble ST2 levels and the effects of nesiritide in acute decompensated heart failure. J Am Coll Cardiol HF 2016;4:68–77.

23. Zhang R, Zhang Y, Zhang J, et al. The prognostic value of plasma soluble ST2 in hospitalized Chinese patients with heart failure. PLoS One 2014;9:e110976.

24. Deeks JJ, Higgins JPT, Altman DG, eds. Chapter 9: analysing data and undertaking meta-analyses. In: Cochrane Handbook for Systematic Reviews of Interventions. Available at: http://handbook.cochrane.org/chapter_9/9_analysing_data_and_undertaking_meta_analyses.htm. Accessed January 13, 2017.

25. Demissei BG, Valente MA, Cleland JG, et al. Optimizing clinical use of biomarkers in high-risk acute heart failure patients. Eur J Heart Fail 2016;18:269–80.

26. Bettencourt P, Azevedo A, Pimenta J, et al. N-terminal-pro-brain natriuretic peptide predicts outcome after hospital discharge in heart failure patients. Circulation 2004;110:2168–74.

27. Sanada S, Hakuno D, Higgins LJ, et al. IL-33 and ST2 comprise a critical biomechanically induced and cardioprotective signaling system. J Clin Invest 2007;117:1538–49.

28. Dieplinger B, Egger M, Koehler W, et al. Prognostic value of soluble ST2 in an unselected cohort of patients admitted to an intensive care unit—the Linz Intensive Care Unit (LICU) study. Clin Chim Acta 2012;413:587–93.

29. Rudolf JW, Lewandrowski EL, Lewandrowski KB, et al. ST2 predicts mortality and length of stay in a critically ill noncardiac intensive care unit population. Am J Clin Pathol 2016;145:203–10.

30. Brunner M, Krenn C, Roth G, et al. Increased levels of soluble ST2 protein and IgG1 production in patients with sepsis and trauma. Intensive Care Med 2004;30:1468–73.

31. Boisot S, Beede J, Isakson S, et al. Serial sampling of ST2 predicts 90-day mortality following

destabilized heart failure. J Card Fail 2008;14:732–8.

32. Henry-Okafor Q, Collins SP, Jenkins CA, et al. Soluble ST2 as a diagnostic and prognostic marker for acute heart failure syndromes. Open Biomarkers J 2012;2012:1–8.

33. Shah KB, Kop WJ, Christenson RH, et al. Prognostic utility of ST2 in patients with acute dyspnea and preserved left ventricular ejection fraction. Clin Chem 2011;57:874–82.

34. Dieplinger B, Gegenhuber A, Kaar G, et al. Prognostic value of established and novel biomarkers in patients with shortness of breath attending an emergency department. Clin Biochem 2010;43:714–9.

35. Socrates T, deFilippi C, Reichlin T, et al. Interleukin family member ST2 and mortality in acute dyspnoea. J Intern Med 2010;268:493–500.

36. Januzzi JL Jr., Peacock WF, Maisel AS, et al. Measurement of the interleukin family member ST2 in patients with acute dyspnea: results from the PRIDE (Pro-Brain Natriuretic Peptide Investigation of Dyspnea in the Emergency Department) study. J Am Coll Cardiol 2007;50:607–13.

37. Aldous SJ, Richards AM, Troughton R, Than M. ST2 has diagnostic and prognostic utility for all-cause mortality and heart failure in patients presenting to the emergency department with chest pain. J Card Fail 2012;18:304–10.

KEY WORDS acute heart failure, meta-analysis, prognosis, sST2

APPENDIX For a supplemental table and figures, please see the online version of this article.