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Prognostic Value of Soluble Suppression of Tumorigenicity-2 in Chronic Heart Failure

A Meta-Analysis

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ABSTRACT

OBJECTIVES The purpose of this study was to perform the first meta-analysis of currently available data.

BACKGROUND Soluble suppression of tumorigenesis 2 (sST2) plasma concentration is elevated in chronic heart failure (CHF) and helps to predict prognosis in this setting, although the evidence is limited.

METHODS Three databases (Medline, Cochrane Library, and Scopus) were searched. Inclusion criteria were: follow-up studies; papers published in English; enrollment of CHF outpatients; available data on hazard ratio (HR) for the $\log_2$ ST2 (so that the reported HRs represent the risk per doubling of sST2) and 95% confidence interval (CI) for all-cause death, and possibly also for cardiovascular (CV) death; and use of standardized sST2 assay. Exclusion criteria were: sST2 considered only as an element of a prognostic score, and studies on patients with end-stage HF.

RESULTS Seven studies were finally included for all-cause death, with a global population of 6,372 patients; data on CV death were available for 5 studies, totaling 5,051 patients. The HR was 1.75 (95% CI: 1.37 to 2.22) for all-cause death and 1.79 (95% CI: 1.22 to 2.63) for CV death (both $p < 0.001$). Significant heterogeneity among studies was detected in the quantification of sST2 predictive value, attributable to marked differences in pharmacological treatment among trials. The predictive power of sST2 was greater when patients were managed according to present guideline-recommended medical treatment.

CONCLUSIONS sST2 is a predictor of both all-cause and CV death in CHF outpatients. The present meta-analysis supports the use of sST2 for risk stratification in patients with stable CHF. (J Am Coll Cardiol HF 2016;■:■–■) © 2016 by the American College of Cardiology Foundation.

Soluble suppression of tumorigenesis 2 protein (sST2) is the circulating form of the cellular receptor ST2L, expressed by cardiomyocytes and vascular endothelial cells together with its ligand interleukin-33 after cardiovascular injury. Binding between interleukin-33 and ST2L is likely to inhibit myocardial hypertrophy and fibrosis and mitigate adverse cardiac remodeling (1,2). sST2 competes with ST2L for interleukin-33 binding, thus likely blunting the cardiovascular protective effects exerted by the interleukin-33/ST2L interaction (1,2).

sST2 has elicited interest as a potential aid to predict prognosis and manage therapy of chronic heart failure (CHF) (3,4). Although the characterization of the

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ABBREVIATIONS AND ACRONYMS

ACEi/ARB = angiotensin-converting enzyme inhibitor or angiotensin receptor blocker

BB = beta-blocker

CHF = chronic heart failure

CI = confidence interval

CV = cardiovascular

HR = hazard ratio

LVEF = left ventricular ejection fraction

MRA = mineralocorticoid receptor antagonist

sST2 = soluble suppression of tumorigenesis 2

interleukin-33/ST2L axis in CHF is currently incomplete (4), sST2 plasma concentrations have been found to be generally higher in CHF patients than in healthy subjects (5). Furthermore, several studies have suggested that higher plasma sST2 concentrations also predict a worse prognosis in CHF patients (6). Accordingly, recent clinical practice guidelines support the use of sST2 assay for risk stratification in CHF outpatients, with a Class IIb, Level of Evidence: B, recommendation (7). Of note, the sST2 assay for risk stratification of acute HF patients was considered Level of Evidence: B (7), reflecting the fact that the prognostic role of sST2 assay in CHF is less well defined than in acute HF (2,6,8), because of the limited number of clinical trials on this topic and the lack of systematic reviews or meta-analyses (7). To fill this gap, we set out to perform a meta-analysis on the prognostic role of sST2 in stable CHF.

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 (9). In March 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."
Inclusion criteria were:

- Follow-up studies, including post hoc analyses of randomized clinical trials;
- Papers in English;
- Enrollment of CHF outpatients (with either reduced or preserved left ventricular ejection fraction);
- Available data, either from papers or from authors, relative to univariate analysis providing median hazard ratio (HR) and to the corresponding 95% confidence interval (CI) for all-cause death, and, possibly, also for cardiovascular (CV) death; and
- The use of last generation, high-sensitivity sST2 assay (Presage ST2 assay, Critical Diagnostics, San Diego, California). At present, this is the only assay that meets the needs of quality specifications of laboratory medicine to have received the Conformitè Européenne Mark and the Food and Drug Administration approval (10).

The exclusion criteria were:

- sST2 not considered per se, but only as an element of a prognostic score; and
- Studies on patients with end-stage HF.

Two reviewers (A.A and G.V.) independently evaluated the studies to be included in the meta-analysis; in case of disagreement, the opinion of a third reviewer (M.E.) was considered.

When a study could not be included only because of lack of crude data on HR and 95% CI, a request was made to the corresponding author to provide the data.

The following data were extracted from each study: first author's last name, publication year, country where the study was conducted, study period, number of patients enrolled, left ventricular ejection fraction (LVEF) criteria, follow-up duration, outcomes evaluated, and all demographic and clinical baseline data provided. The data were extracted by a reviewer (A.A.), and were checked for accuracy by a second reviewer (G.V.).

STATISTICAL ANALYSIS. Statistical analysis was performed using the R statistical software (version 3.2.3, 2015; *metaphor* package, R Foundation for Statistical Computing, Vienna, Austria) (11).

The HRs for all-cause and CV death with the corresponding 95% CI were recorded; in all cases, the HRs were calculated for the $\log_2$ST2, 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, the log10 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 allowed to calculate global log(HR) with its 95% CI. The z statistic was used to evaluate the null hypothesis (sST2 values are not predictive of either all-cause or CV death). The corresponding p value was calculated; a p value <0.05 was considered significant.

The heterogeneity analysis was compatible only with the random-effects model. Due to the small number of studies, the Cochran's Q test was not employed (13). The following measures were calculated: tau^2 (estimated amount of total heterogeneity), tau (square root of tau^2), I^2 (total heterogeneity/total variability), H^2 (total variability/sampling variability), and H (square root of H^2); the 95% CI was calculated

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