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Prognostic Value of Baseline and Changes in Circulating Soluble ST2 Levels and the Effects of Nesiritide in Acute Decompensated Heart Failure

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ABSTRACT

OBJECTIVES The study sought to investigate the association between soluble growth stimulation expressed gene 2 (sST2) level and adverse outcomes in acute heart failure (HF).

BACKGROUND Several studies have demonstrated the prognostic utility of sST2 levels in HF.

METHODS sST2 levels were measured in sequential baseline and follow-up (48 to 72 h and 30 days) plasma samples from 858 acute HF subjects enrolled in the ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) trial biomarker substudy and were related to in-hospital and post-discharge clinical outcomes.

RESULTS Higher sST2 levels were associated with increased death risk at 180 days (baseline hazard ratio [HR]: 2.21; follow-up HR: 2.64; both $p < 0.001$). These results were not independent of covariates and aminoterminal pro-B-type natriuretic peptide for baseline sST2 (HR: 1.29, $p = 0.243$), but were borderline significant for follow-up sST2 (HR: 1.61, $p = 0.051$). Subjects with persistently high (>60 ng/ml) sST2 levels at follow-up had higher 180-day death rates than those with lower follow-up sST2 levels (adjusted HR: 2.91, $p = 0.004$). Neither baseline nor follow-up sST2 levels were associated with dyspnea improvement. Changes in sST2 from baseline were less in the nesiritide versus placebo group at follow-up, but were similar at 30 days.

CONCLUSIONS Elevated levels of sST2 were associated with an increased risk of adverse clinical events in acute HF, but prognostic value of baseline sST2 diminished after adjusting for clinical covariates and aminoterminal pro-B-type natriuretic peptide. In those with elevated baseline sST2 levels, persistently elevated sST2 levels at follow-up were associated with increased mortality risk. In addition, nesiritide did not demonstrate an incremental impact on sST2 levels over standard therapy. (J Am Coll Cardiol HF 2016;4:68–77) © 2016 by the American College of Cardiology Foundation.

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Growth stimulation expressed gene 2 (ST2) is a transmembrane protein and a member of the Toll-interleukin 1 receptor superfamily (1,2). ST2 binds interleukin-33 in response to cardiac disease or injury and elicits a cardioprotective effect by mitigating the maladaptive responses of the myocardium to overload states (3,4). A truncated soluble form of ST2 (soluble ST2 [sST2]) competes with the membrane-bound form in this interleukin-33 binding. Elevated levels of sST2 signal the presence and severity of adverse cardiac remodeling and tissue fibrosis, which may occur in response to an acute coronary syndrome event or worsening heart failure (HF) (3,5). Higher levels of sST2 are associated with more severe clinical symptoms and with other objective measures of HF severity, such as higher C-reactive protein, higher natriuretic peptide levels, lower left ventricular ejection fraction, and higher diastolic filling pressures (6–12). Elevated circulating sST2 levels have been associated with an increased risk for mortality and sudden cardiac death in outpatients with HF (9,13–15), as well as in acute HF (16). However, most studies have only measured sST2 at a single timepoint (predominantly at baseline) and only described the relationship with long-term all-cause mortality.

In this post-hoc study utilizing blood specimens collected serially in the ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) trial, we examined the relationship between baseline and serial levels of sST2 and dyspnea status, hospitalization (at 30 days), and death (at 180 days). We also examined the effect of nesiritide therapy on sST2 levels, hypothesizing that the vasodilatory effects of nesiritide may relieve volume overload more effectively than a placebo, thereby potentially achieving greater reduction in sST2 levels.

METHODS

STUDY POPULATION. Details of the ASCEND-HF Trial (NCT00475852) have been described elsewhere (17). Briefly, this was a multinational, multicenter, prospective randomized controlled trial of 7,141 subjects presenting with signs and symptoms of acute decompensated HF comparing nesiritide (a recombinant B-type natriuretic peptide with vasodilatory properties) to placebo added to standard care. In our study cohort, 858 subjects (12% of the total population) consented to participate in the biomarker substudy. A large majority of subjects in the biomarker substudy were recruited from North American sites (n = 824). Compared to the rest of the North American study cohort (n = 2,419), there were no differences in race (p = 0.422), heart rate (p = 0.157), atrial fibrillation (p = 0.124), blood urea nitrogen (p = 0.384), creatinine (p = 0.499), time to randomization (p = 0.051), or beta-blockers (p = 0.073). Nevertheless, age (66.6 ± 14.9 vs. 64.5 ± 15.4 years, p = 0.001) and left ventricular ejection fraction (31.6 ± 15 vs. 30.4 ± 15, p = 0.035) were significantly different.

ABBREVIATIONS AND ACRONYMS

CI = confidence interval
HF = heart failure
HR = hazard ratio
IQR = interquartile range
NT-proBNP = aminoterminal pro-B-type natriuretic peptide
OR = odds ratio
sST2 = soluble growth stimulation expressed gene 2

STUDY DESIGN. The intent of the biomarker substudy was to collect venous blood samples at randomization ("baseline"), 48 to 72 h following randomization, and at the 30-day follow-up visit. Blood samples were collected in ethylenediaminetetraacetic acid-plasma, immediately centrifuged at the study sites, and stored at -80°C for subsequent analysis at a central core laboratory. Aminoterminal pro-B-type natriuretic peptide (NT-proBNP) levels were determined by the VITROS NT-proBNP Assay (Ortho-Clinical Diagnostics, Raritan, New Jersey).

SOLUBLE ST2 ASSAY. Plasma sST2 levels were measured by the Presage ST2 Assay (Critical Diagnostics, San Diego, California) at a College of American Pathologists/Clinical Laboratory Improvements Amendments-approved core laboratory independent of the sponsors. This is a quantitative sandwich enzyme-linked immunosorbent assay using a mouse monoclonal antihuman sST2 capture antibody on microtiter plate wells and a second biotinylated mouse monoclonal antihuman sST2 tracer antibody with a measuring range of 3.1 to 200 ng/ml

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